The pursuit of user-friendly medicines:

Older people in the hot seat

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Older people in the hot seat

Bevorderen van gebruiksvriendelijke geneesmiddelen: ouderen aan zet
(met een samenvatting in het Nederlands)

Proefschrift

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Chapter 1

General introduction

Medication use

Medicines play a key role in the diagnosis, treatment and prevention of diseases, they slow down or halt disease progression and ease symptoms of diseases. For a medicine to work properly though, it has to be used correctly, i.e. at the right dose, at the right time and by the right directions. Using medicines is, however, a complex process. There are many different routes of administration available, and the use of medicines involves a variety of tasks including the reading and understanding of the user information, removing the medicine from the outer and inner packaging, any preparation before use, and last of all, administration of the medicine.

People may experience difficulties with any of these activities, for instance with the opening of packaging or with the breakability of tablets.[1, 2] Such practical issues may reduce a patient's confidence in the quality of a product and ultimately affect adherence. Moreover, difficulties with the use of medicines may lead to over- or underdosing and can cause serious injury. For example, inappropriate use of measuring devices for the administration of oral liquids may lead to under- or overdosing[3, 4], tablets may be swallowed within their blisterpacks, causing oesophageal and intestinal perforations[5-15], and the erroneous use of transdermal patches, for instance the administration of an incorrect dose or administration at the wrong time, has been shown to cause adverse events.[16-18] Also, incorrect storage of the medicinal product can be detrimental to a product's quality and affect the efficacy and safety of the medicinal product.[19, 20]

Interaction between patient and medicinal product

A successful interaction between patient and medicinal product is essential for a medicine to be used correctly. The interaction between patient and medicinal product is dependent on the complexity of the use of a medicine and the patient's capability to carry out the required tasks. For example, one of the most important requirements for adequate efficacy of tablets and capsules is the patient's ability to swallow them. If a tablet needs to be subdivided to obtain the prescribed dose, a patient should understand and remember this, and be able to perform this task. Another example is the use of transdermal anticholinergic patches for dementia. These patches should be worn continuously for a specified time period after which they should be removed and a new patch should be applied to a different skin site. This medicine demands that a patient or his caregiver has adequate cognitive ability to remember site and time of patch application and removal. The complexity of use of a medicine is defined by its physical properties, such as its pharmaceutical form or the

packaging it is presented in. In general, a tablet can be considered less complex to use than an inhalation product. Patient characteristics such as physical and mental health determine the capability of the patient to perform the required tasks to use the medicine.

The challenges of pharmacotherapy in older people

Pharmaceutical care becomes more complicated with advanced age because the characteristics and health problems of older people are different and often more complex than those of younger adults. For instance, the effect of a treatment can be different in older people because aging comes with physiological changes that alter medication response. Additionally, the increased prevalence of comorbidities and use of multiple medicines will render older people more susceptible for adverse drug reactions compared to young adults. Current incentives to improve pharmacotherapy in the geriatric population mostly focus on inappropriate prescribing. Older people are often underrepresented in clinical trials, even in trials studying treatments for conditions which especially affect older people, i.e. treatment for cancer, Alzheimer's disease, Parkinson's disease, incontinence, and cardiovascular disease. The poor representation of older people from clinical trials limits the generalisability of the efficacy and safety findings to the older population, and hinders evidence-based clinical decision-making in these high-risk people. In the Netherlands, 20% of the older people in primary care are prescribed potentially inappropriate medications.[21-31]

A relatively unwatched factor that affects pharmacotherapy in older people is the practical problems that older people may experience with the use of their medicines. Aging comes with functional decline, e.g. with regard to vision, hearing, manual dexterity and hand-grip strength, and the prevalence of disabilities such as dysphagia, arthritis or tremors is higher among older adults. Consequently, aging can affect a patient's ability to use medicines as required. It can become more difficult to handle medication packaging, to swallow medicines, and to adequately use an inhaler or apply eye drops. Concurrently, older people often suffer from multiple chronic conditions, and they may therefore use multiple medicines. In the Netherlands, approximately 45% of the people aged over 65 years take at least five different medicines. Nearly 20 percent of patients over 75 years take as many as ten or more medicines.[32] The use of multiple medicines, polypharmacy, increases the complexity of medication regimens. For instance, some medicines have to be taken three times a day and others once or twice a day, some have to be taken on an empty stomach and others after a meal. Some medicines need to be dissolved or broken before use, others need to be inhaled or applied topically.[33] Complicated medication regimes are difficult to adhere to and require sufficient motivation and adequate cognitive skills from the patient.

A reduction in cognitive skills will compromise the correct and timely use of medicines e.g. by forgetting to take medicines and unintended changes to the medication schedule.[1, 34-38] In addition, poor health literacy, i.e. failure to obtain, read, understand, and appraise use related information necessary to make appropriate health decisions and follow instructions for treatment, is frequently observed among older people. The main explanation to low health literacy among older people is a decline cognitive function.[39-42] A recent systematic review addressing the relationship between health literacy and medication adherence showed an association between better health literacy and increased medication adherence.[43] Furthermore, changes in social factors, e.g. family status, loneliness and communication skills can hinder older patients in receiving assistance when needed.

Older people as starting point for the development of user-friendly medicines

The aging of the population increases the number of people that require long-term care services for a longer period of time, which presents several challenges to our health and social care expenditures. European health policy therefore encourages people to live longer independently in their own homes and aims to increase peoples' responsibility in managing their own health.[44-46] The ability of older patients to manage their own health partly depends on their ability to adequately manage their medication.

Medication management requires cognitive and functional capacities to coordinate and carry out the task associated with the use of medicines. It is evident that older people are more prone to incorrect use of medicines compared to younger adults. Preliminary research suggests that practical problems with the use of medicines, such as problems with swallowing or opening medication packaging, have a considerable influence on the self-management ability and medication adherence of older patients.[38, 47-50] Non-adherence to a medication regimen may result in a suboptimal therapeutic effect or more side effects, resulting in the loss of autonomy, disease progression, use of additional medicines, nursing home placement or hospitalisation.[51, 52] Health care professionals play an important role in preventing any problems with the use of medicines by providing appropriate, understandable and relevant information to patients about the use of their medicines. However, it is unreasonable to expect that health care professionals can completely fill the gap between the complexity of the use of a medicine and the patient's capability of understanding and performing the required actions to use the medicine.

Taking the capabilities of the aging population into account during the development of a medicine is key to improving the interaction between the patient and the medicinal product and of paramount importance to a patient's self-management ability. Not only older people will benefit from this, it will make medicines more user-friendly within the entire population. Research on the difficulties that older people experience using their medicines is very fragmented and does not address all tasks a patient has to complete to use a medicine. Further insight into the practical problems older people encounter using their medications will enhance the development of more user-friendly medicines. This knowledge is relevant for developers of medicinal products as well as in the context of regulatory science.[53]

Conclusions

The use of medicines is a complex task during which many difficulties can be experienced. These difficulties can affect adherence, cause over- or underdosing and may even result in serious injury. Aging comes with an increased prevalence of issues that affect the ease and correct use of medicines. Furthermore, older people are the largest user group of medicines. To improve the user-friendliness of medicines, the capabilities of the aging population should be taken into account during the development of medicines.

Objectives of this thesis

The objectives of this thesis are to provide insight in the problems that older people experience with the daily use of their medicines, to investigate the suitability of the design of medicines for older people and to explore approaches to prevent the occurrence of usability problems.

Outline of this thesis

This thesis consists of three sections. **Chapter 2** focuses on the practical problems that older people experience with the daily use of their medication. Chapter 2.1 describes the prevalence of problems with opening medicine packaging in the elderly. Chapter 2.2 presents a qualitative analysis of practical problems that older people experience using their medicines, the management strategies they apply to overcome these problems and the potential clinical relevance of these problems and management strategies.

The studies reported in **Chapter 3** focus on the suitability of the design of medicines for use by older people. In Chapter 3.1 we compared the ability of older people to break scored tablets with that of young adults. In Chapter 3.2 the design features of medicines that were related to practical problems with medication use in daily practice were investigated.

Chapter 4 focusses on the prevention of usability problems with medicines. Chapter 4.1 describes the attention of pharmacy technicians to problems with opening medicine packaging. Chapter 4.2 focuses on the development of in vitro studies for the investigation of safe mixing of solid oral medicines with food to overcome swallowing problems. In chapter 4.3 we investigated methods to evaluate the performance of score marks.

Finally, the results of these studies are summarised and put into a broader perspective in **Chapter 5** with the aim to provide recommendations to improve the user-friendliness of medicines.

References

1. van Geffen EC, Meuwese E, Philbert D, Bouvy ML. Problems with medicine packages: Experiences reported to a dutch medicine reporting system. Ann Pharmacother. 2010;44(6):1104-9
2. Rodenhuis N, de Smet PA, Barends DM. Patient experiences with the performance of tablet score lines needed for dosing. Pharm World Sci. 2003;25(4):173-6
3. Hyam E, Brawer M, Herman J, Zvieli S. What's in a teaspoon? Underdosing with acetaminophen in family practice. Family practice. 1989;6(3):221-3
4. Ryu GS, Lee YJ. Analysis of liquid medication dose errors made by patients and caregivers using alternative measuring devices. Journal of managed care pharmacy: JMCP. 2012;18(6):439-45
5. Bosson V, Schnyder JM, Tschopp JM. [foreign bodies and hemoptysis: About danger of ingesting blister-wrapped tablets]. Rev Med Suisse. 2011;7(290):798-801
6. Campos Franco J, Lopez Rodriguez R, Martinez De Alegria A, Dios Loureiro C, Alende Sixto R, Gonzalez Quintela A. [esophageal perforation after ingestion of a blister-wrapped tablet]. Gastroenterol Hepatol. 2011;34(7):515-6
7. Campos-Franco J, Vallejo-Senra N, Martin Carreras-Presas FL, Lopez-Rodriguez R, Dominguez-Santalla MJ, Alende-Sixto R. Gastric hemorrhage after ingestion of a blister-wrapped tablet. Gastroenterol Hepatol. 2017;40(1):18-9
8. Coulier B, Rubay R, Van den Broeck S, Azar AR, Maldague P, Mailleux P*, et al.* Perforation of the gastrointestinal tract caused by inadvertent ingestion of blister pill packs: Report of two cases diagnosed by mdct with emphasis on maximal intensity and volume rendering reformations. Abdom Imaging. 2014;39(4):685-93
9. Fulford S, Tooley AH. Intestinal perforation after ingestion of a blister-wrapped tablet. Lancet. 1996;347(8994):128-9
10. Laeeq SM, Rai AA, Tasneem AA, Luck NH, Majid Z. Pill in the blister pack: A rare cause of dysphagia in an elderly adult. Pan Afr Med J. 2015;22:176
11. Gupta V, Manikyam SR, Gupta R, Gupta NM. Pelvic abscess after ingestion of blister-wrapped tablet. Am J Gastroenterol. 2002;97(8):2142-3
12. Purnak T, Ozaslan E, Efe C. Concomitant oesophageal perforation and bleeding due to a tiny pill with its blister pack. Age Ageing. 2011;40(5):645-6
13. Prokop A, Stepper H, Koll S, Chmielnicki M. [no blister-wrapped pills: Perforation after ingestion a blister-pack]. Z Orthop Unfall. 2016;154(3):299-302
14. Yao SY, Matsui Y, Shiotsu S. An unusual case of duodenal perforation caused by a blister pack: A case report and literature review. Int J Surg Case Rep. 2015;14:129-32
15. Al-Ramahi G, Mohamed M, Kennedy K, McCann M. Obstruction and perforation of the small bowel caused by inadvertent ingestion of a blister pill pack in an elderly patient. BMJ Case Rep. 2015;2015
16. Grissinger M. Fentanyl transdermal patches: More protection needed for patients and their families. Pharmacy and Therapeutics. 2009;34(7):343-90
17. Lövborg H, Holmlund M, Hägg S. Medication errors related to transdermal opioid patches: Lessons from a regional incident reporting system. BMC Pharmacol Toxicol. 2014;15:31
18. In brief: Heat and transdermal fentanyl. Med Lett Drugs Ther. 2009;51(1318):64
19. Renswouw DC, Laarhoven AC, Haren MJ, Bouvy ML, Weda M. Storage instructions for inhalation capsules: Consequences of incorrect storage and adherence in daily practice. J Pharm Pract. 2010;23(6):548-52
20. Stollberger C, Finsterer J. Concerns about storage and application of dabigatran and rivaroxaban. Eur J Clin Pharmacol. 2013;69(3):739-40
21. Dodd KS, Saczynski JS, Zhao Y, Goldberg RJ, Gurwitz JH. Exclusion of older adults and women from recent trials of acute coronary syndromes. J Am Geriatr Soc. 2011;59(3):506-11
22. Fitzsimmons PR, Blayney S, Mina-Corkill S, Scott GO. Older participants are frequently excluded from parkinson's disease research. Parkinsonism Relat Disord. 2012;18(5):585-9
23. Green P, Maurer MS, Foody JM, Forman DE, Wenger NK. Representation of older adults in the late-breaking clinical trials american heart association 2011 scientific sessions. J Am Coll Cardiol. 2012;60(9):869-71

24. Scher KS, Hurria A. Under-representation of older adults in cancer registration trials: Known problem, little progress. J Clin Oncol. 2012;30(17):2036-8
25. Mitchell SL, Sullivan EA, Lipsitz LA. Exclusion of elderly subjects from clinical trials for parkinson disease. Arch Neurol. 1997;54(11):1393-8
26. Cherubini A, Oristrell J, Pla X, Ruggiero C, Ferretti R, Diestre G*, et al.* The persistent exclusion of older patients from ongoing clinical trials regarding heart failure. Arch Intern Med. 2011;171(6):550-6
27. Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in clinical trials for cancer drug registration: A 7-year experience by the us food and drug administration. J Clin Oncol. 2004;22(22):4626-31
28. Morse AN, Labin LC, Young SB, Aronson MP, Gurwitz JH. Exclusion of elderly women from published randomized trials of stress incontinence surgery. Obstet Gynecol. 2004;104(3):498-503
29. Cohen-Mansfield J. Recruitment rates in gerontological research: The situation for drug trials in dementia may be worse than previously reported. Alzheimer Dis Assoc Disord. 2002;16(4):279-82
30. Crome P, Lally F, Cherubini A, Oristrell J, Beswick AD, Clarfield AM*, et al.* Exclusion of older people from clinical trials: Professional views from nine european countries participating in the predict study. Drugs Aging. 2011;28(8):667-77
31. Beers E, Moerkerken DC, Leufkens HG, Egberts TC, Jansen PA. Participation of older people in preauthorization trials of recently approved medicines. J Am Geriatr Soc. 2014;62(10):1883-90
32. Dijk C, Verheij R, Schellvis F. Huisartsenzorg in cijfers: Polyfarmacie bij ouderen. Huisarts en Wetenschap. 2009;52(7):315
33. Lehnert T, Heider D, Leicht H, Heinrich S, Corrieri S, Luppa M*, et al.* Review: Health care utilization and costs of elderly persons with multiple chronic conditions. Med Care Res Rev. 2011;68(4):387-420
34. Tordoff JM, Bagge ML, Gray AR, Campbell AJ, Norris PT. Medicine-taking practices in community-dwelling people aged > or =75 years in new zealand. Age Ageing. 2010;39(5):574-80
35. Stegemann S, Ecker F, Maio M, Kraahs P, Wohlfart R, Breitkreutz J*, et al.* Geriatric drug therapy: Neglecting the inevitable majority. Ageing Res Rev. 2010;9(4):384-98
36. Mehuys E, Dupond L, Petrovic M, Christiaens T, Van Bortel L, Adriaens E*, et al.* Medication management among home-dwelling older patients with chronic diseases: Possible roles for community pharmacists. J Nutr Health Aging. 2012;16(8):721-6
37. Kelly J, D'Cruz G, Wright D. Patients with dysphagia: Experiences of taking medication. J Adv Nurs. 2010;66(1):82-91
38. Kairuz T, Bye L, Birdsall R, Deng T, Man L, Ross A*, et al.* Identifying compliance issues with prescription medicines among older people: A pilot study. Drugs Aging. 2008;25(2):153-62
39. Kobayashi LC, Wardle J, Wolf MS, von Wagner C. Aging and functional health literacy: A systematic review and meta-analysis. J Gerontol B Psychol Sci Soc Sci. 2014
40. Sorensen K, Van den Broucke S, Fullam J, Doyle G, Pelikan J, Slonska Z*, et al.* Health literacy and public health: A systematic review and integration of definitions and models. BMC Public Health. 2012;12:80
41. Boyle PA, Yu L, Wilson RS, Segawa E, Buchman AS, Bennett DA. Cognitive decline impairs financial and health literacy among community-based older persons without dementia. Psychol Aging. 2013;28(3):614-24
42. Federman AD, Sano M, Wolf MS, Siu AL, Halm EA. Health literacy and cognitive performance in older adults. J Am Geriatr Soc. 2009;57(8):1475-80
43. Zhang NJ, Terry A, McHorney CA. Impact of health literacy on medication adherence: A systematic review and meta-analysis. Ann Pharmacother. 2014;48(6):741-51
44. Europe in figures - online eurostat yearbook [Internet]. European Commission. 2013 [cited 22 August 2014]. Available from: http://epp.eurostat.ec.europa.eu/statistics_explained/index.php/Population_structure_and_ageing.
45. OECD. Health at a glance: Europe 2014. 2014.
46. European commission. The 2012 ageing report: Economic and budgetary projections for the 27 eu member states (2010-2060). Brussels: European Economy; 2012.

47. Kripalani S, Henderson LE, Chiu EY, Robertson R, Kolm P, Jacobson TA. Predictors of medication self-management skill in a low-literacy population. J Gen Intern Med. 2006;21(8):852-6
48. Overgaard AB, Hojsted J, Hansen R, Moller-Sonnergaard J, Christrup LL. Patients' evaluation of shape, size and colour of solid dosage forms. Pharm World Sci. 2001;23(5):185-8
49. Atkin PA, Finnegan TP, Ogle SJ, Shenfield GM. Functional ability of patients to manage medication packaging: A survey of geriatric inpatients. Age Ageing. 1994;23(2):113-6
50. Ruscin JM, Semla TP. Assessment of medication management skills in older outpatients. Ann Pharmacother. 1996;30(10):1083-8
51. Swanlund SL, Scherck KA, Metcalfe SA, Jesek-Hale SR. Keys to successful self-management of medications. Nurs Sci Q. 2008;21(3):238-46
52. Hanlon JT, Schmader KE, Semla TP. Update of studies on drug-related problems in older adults. J Am Geriatr Soc. 2013;61(8):1365-8
53. Gispen-de Wied CC, Leufkens HG. From molecule to market access: Drug regulatory science as an upcoming discipline. Eur J Pharmacol. 2013;719(1-3):9-15

Chapter 2

The experiences of older people with medication use

2.1

Chapter 2.1

Problems experienced by older people when opening medicine packaging

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Abstract

Objective

Medicine packages can cause problems in daily practice, especially among older people. This study aimed to investigate the prevalence of problems experienced by older people when opening medicine packaging and to investigate how patients manage these problems.

Methods

A convenience sample of 30 community pharmacies participated in this study. They selected a systematic sample of 30 patients over 65 years old with a recent omeprazole prescription, and a questionnaire was administered by telephone for at least 10 patients per pharmacy.

Key findings

A total of 317 patients completed the questionnaire. They received their omeprazole in a bottle (n = 179, 56.5%), push-through blister pack (n = 102, 32.2%) or peel-off blister pack (n = 36, 11.4%). Some 28.4% of all patients experienced one or more problems with opening their omeprazole packaging; most problems occurred with peel-off blisters (n = 24, 66.7% of all respondents using peel-off blisters), followed by push-through blisters (n = 34, 33.3%) and finally bottles (n = 32, 17.9%). The risk of experiencing problems with peel-off blisters and push-through blisters was higher [relative risk 3.7 (95% confidence interval 2.5–5.5) and 1.9 (1.2–2.8), respectively] than the risk of experiencing problems with opening bottles. Two-thirds of respondents reported management strategies for their problems. Most were found for problems opening bottles (n = 24, 75%), followed by push-through blisters (n = 24, 70.6%) and peel-off blisters (n = 14, 58.3%).

Conclusions

One in four patients over 65 experienced difficulties opening their omeprazole packaging and not all of them reported a management strategy for their problems. Manufacturers are advised to pay more attention to the user-friendliness of product packaging. In addition, it is important that pharmacy staff clearly instruct patients on how to open their medicine packaging, or assist them in choosing the most appropriate packaging.

Introduction

Previous research suggests that medicine packages cause considerable problems in daily practice. Most of the practical problems reported concern the opening of medication packaging and the removal of medicines from packaging. Nearly half the complaints relate to opening blister packs, but problems with opening other packaging types are also reported.[1]

Impaired vision, hand strength and dexterity cause difficulties with opening medicine packages in older people.[2-4] Such medication-use problems can decrease medication adherence, especially when these problems affect the patient's self-management ability.[5, 6] Older people are more likely to have problems with dexterity and visual acuity, and also have multimorbidity, and might be on polypharmacy regimes. They are therefore more likely to be non-adherent and experience the negative effects of poor disease control.[7] Further analysis of the data from our previous study[1] showed that patients most frequently mentioned problems with opening the packaging of the proton-pump inhibitor omeprazole. Omeprazole is among the most commonly used drugs in the Netherlands, especially among older people.[8, 9] It is available as both capsules and tablets, which are packaged in bottles and push-through and peel-off blister packs. All primary packaging of omeprazole is aimed at reducing exposure to humidity. Most commonly, omeprazole is dispensed in a push-through blister consisting of two layers: aluminium foil with cavities shaped to contain the medicine and an overlying foil through which the medicine should be pushed in order to extract it. The peel-off blister is dispensed less frequently and looks similar to the push-through blister, but instead of pushing the medicine through the foil, the foil (often aluminium laminated with polyester) has a pull tab for peeling it off and opening the cavity. The strong, laminated aluminium in this type of foil prevents pushing through.

The generic availability of a wide range of omeprazole labels increases the likelihood that patients will receive their omeprazole in various types of packaging over time. These different medicine packages may require a different way of opening or removal of the tablets or capsules, of which the patient might not be aware.

Although we previously found a high proportion of spontaneous reports by patients concerning medication packaging[1], the exact prevalence of packaging problems remains unknown. Moreover, it is unclear how and to what extent patients are able to manage these problems. Because of the variety in packaging types and the high occurrence of difficulties, investigating problems with omeprazole packaging is likely to yield a high number of varied issues. Therefore the aim of this study was to investigate the prevalence of problems with opening omeprazole medicine packaging in individuals over 65 years of age, and how they manage these problems.

Methods

The study was conducted in compliance with the requirements of the Utrecht Pharmacy Practice network for Education and Research (UPPER) institutional review board of the Division of Pharmacoepidemiology and Clinical Pharmacology. The study was approved by the board on 11 December 2009.

In this cross-sectional study we conducted a telephone questionnaire with patients aged 65 years and older who were using the proton-pump inhibitor omeprazole, to explore the problems experienced with opening medicine packages.

Setting

The setting was community pharmacy. Data was collected by a convenience sample of 30 pharmacies belonging to UPPER, selected because they were supervising pharmacy student interns during the period of data collection. These pharmacies covered areas in the central, northwest and southwest parts of the Netherlands, in mostly urban settings.

Patients

Between December 2009 and April 2010 pharmacy staff (aided by pharmacy students) in the participating pharmacies selected, from the automated dispensing records, all patients born before 1 January 1945 who had presented a prescription for omeprazole (ATC A02BC01) after 1 September 2009. From the resulting list a systematic sample of 30 patients was chosen in each pharmacy (e.g. if the selection resulted in 300 patients, one patient in every 10 consecutive patients on the list was chosen and if the selection resulted in 120 patients, one in every four was chosen). Patients who received their medication in special pill organisers, or who were known not to manage their own medication (e.g. living in a nursing home or mental care institution), were excluded by the pharmacist.

Procedure

Pharmacists mailed selected patients a letter with information on the aim and procedure of the study. Patients were asked to inform the pharmacy within a week if they did not want to participate. A week after sending the letters pharmacy staff started to contact the remaining patients by telephone, and after confirming verbal consent to take part administered the questionnaire over the telephone. Because it is not possible to make a sample-size calculation, we aimed to include at least 300 patients to be able to obtain a large number and representative range of experiences. To attain this number of respondents we asked pharmacy employees to continue to contact patients until they had collected at least 10 completed questionnaires. Pharmacies recorded how many patients were contacted by phone and the reasons for non-response or refusal to participate.

Questionnaire

The questionnaire contained questions regarding sociodemographic characteristics (age, gender, native language, level of education), omeprazole packaging and whether or not they had ever experienced problems with opening an omeprazole package (if yes, they were asked to describe these problems, in free text, and any solution). The questionnaire was tested for face validity by other academics (co-workers).

Questionnaire data was stored and analysed using SPSS for Windows, version 19.0. Age, gender and education level were categorised and compared between patients with and without problems using Chi-square analysis. For the open ended questions the answers were clustered per packaging type and per problem or solution (i.e. different phrasings that mentioned the same issue or solution, such as 'using a letter opener' and 'using pliers'), and summarised into a category title (such as 'use of improvised tools'; see also Tables 2 and 3, below). Categories were compiled by one researcher (DP) and checked by a second (EvG). Relative risks of having problems with different packaging types were calculated (using containers as a reference group).

Results

Pharmacies contacted the patients from their list of 30 until they had obtained at least 10 completed questionnaires, so it is possible that not all of the eligible patients needed to be phoned. In total 401 patients were reached by telephone starting a week after the letter had been sent, at which point another 84 patients declined to participate. Reasons given were: 'I don't feel like it'/'I don't have time' or 'I never take part in research', or there were language problems that made a phone questionnaire too difficult. Finally, 317 (79% of those contacted) patients completed the questionnaire. Table 1 shows the respondents' characteristics.

Table 1 Patient characteristics

Characteristics	**n (%)**
Female gender	216 (67.8)
Age (years) (mean 74)	
65-74	188 (59.3)
75-85	108 (34.1)
≥86 or >85	21 (6.6)
Education	
None/primary school	199 (62.8)
Secondary school	59 (18.6)
College/university	40 (12.6)
Other/unknown	19 (6.0)
Native language other than Dutch	9 (2.8)

Of the 317 participants, 179 (56.5%) reported receiving their omeprazole medication in a bottle [possible caps included tamper-evident lids or screw caps (tear-away rings), aluminium or foil liners and child-resistant closures], 102 (32.2%) in a push-through blister pack and 36 (11.4%) in a peel-off blister. Ten people mentioned previously receiving their omeprazole in different packaging and 90 patients (28.4%) indicated they had experienced problems with opening the omeprazole package. A total of 95 problems were reported. There was no difference in distribution of age, gender or education level in patients with and without problems.

Table 2 lists the types of problem with opening omeprazole packaging that patients described. Of the 90 respondents who experienced problems opening their omeprazole packaging, 62 (68.9%) described a total of 68 management strategies to overcome packaging problems. Proportionally, most problems occurred with opening peel-off blisters (n = 24, 66.7% of all respondents using peel-off blisters), followed by push-through blisters (n = 34, 33.3%). Patients who received omeprazole in a bottle/ container reported the fewest problems with opening the package (n = 32, 17.9%). The risk of experiencing one or more problems with opening peel-off-blisters was almost four times higher (relative risk 3.7, 95% confidence interval 2.5–5.5) and that with push-through blisters was almost twice as high (relative risk 1.9, 95% confidence interval 1.2– 2.8) than the risk of experiencing a problem with opening bottles.

Table 3 lists the management strategies described by patients to solve their problems. When specifically asked, 16 out of 90 respondents (17.8%) said they received help from their partner (n = 9), family/ neighbours (n = 5), a professional carer (n = 1) or the pharmacy (n = 1). Most help was received for problems with bottles or containers; nine patients (28.1% of patients with problems with this packaging type) reported receiving help.

Table 2 Problems reported with omeprazole packaging			
Type of problem	**Bottles/containers** N = 32/179 patients n (%)*	**Push-through blister** N = 34/102 patients n (%)†	**Peel-off blister** N = 24/36 patients n (%)
The lid/screw cap is difficult to remove	11 (6.1)	-	-
First-time-use tamper-evident lid/ screw cap: difficult to remove	11 (6.1)	-	-
First-time-use tamper-evident aluminium/foil liner: difficult to remove	8 (4.5)	-	-
The child-resistant closure is difficult to open	5 (2.8)	-	-
Aluminium/plastic is too firm	-	15 (14.7)	-
Unable/difficult to remove medicine	-	9 (8.8)	16 (44.4)
Medicine breaks or crumbles when pushed through	-	7 (6.9)	-
Other (cavity too small for medicine to go through, space around medicine too large, cavities too close to each other to push, blister pack too pliable)	-	5 (4.9)	-
When peeling, more than one cavity is opened	-	-	2 (5.6)
Pull tab is too small to grasp	-	-	2 (5.6)
Impossible to push through/ it doesn't say how it should be opened	-	-	4 (11.1)

*32 patients reported 35 problems.
†34 patients reported 36 problems.

Table 3 Management strategies			
Type of strategy	**Bottles/containers** N = 24 (out of 32) n (% of patients with problems)*	**Push-through blister** N = 24 (out of 34) n (% of patients with problems)*	**Peel-off blister** N = 14 (out of 24) n (% of patients with problems)*
Household tools (e.g. scissors, knife or pliers)	11 (34.4)	10 (29.4)	8 (33.3)
Trying again/finding a handy way	6 (18.8)	1 (2.9)	2 (8.3)
Asking someone else	6 (18.8)	4 (11.8)	1 (4.2)
Using an appropriate tool (e.g. screw-cap opener)	3 (9.4)	-	-
Transferring all the medicines to a container (usually by themselves)	-	11 (32.4)	5 (20.8)
No strategies reported	8 (25.0)	10 (29.4)	10 (41.7)

*Some patients reported having more than one strategy, so the total percentage might exceed 100%.

Discussion

Main findings

In this large cross-sectional study we found that one out of four omeprazole users aged 65 years or older experienced problems with opening their packaging, and that not all patients were able to satisfactorily manage these problems. A third of the patients with problems (one out of eight patients in the total study population) did not report any management strategy to overcome their problems. Fewer management strategies were found for the problems experienced with peel-off blisters compared to the other packaging systems, and the strategies applied by people to open these blisters more often included the use of inappropriate or even slightly dangerous tools, such as scissors or knives.

Strengths and limitations

The strength of this study was that we were able to establish the prevalence of packaging problems in a large cross-section of patients, demonstrating that these problems occur frequently. Our study has some limitations. First the type of blister package the patients were actually using was self-reported and this was not validated. Several patients indicated that the aluminium foil was too firm to push the medicine through, but it could be that some of these medicines were packaged in a peel-off blister pack without the patient's knowledge. If this was the case, however, it supports our recommendation that patients need better instructions, both written and verbal, on how to remove their medicine from its packaging.

Another limitation is that patients were not asked how the problem affected the actual use of their medication. For example, we do not know whether the problems lead to incidental skipping of one or more doses. Therefore, we cannot definitely conclude that packaging problems have an impact on medication adherence.

Implications for practice

Patients using peel-off blisters and push-through blisters more often experienced problems than patients using bottles, and peel-off blisters caused the most problems. A recent study also demonstrated the relative difficulty of opening peel-off blisters compared to push-through blisters.[10] Problems that are related to the opening of peel-off blisters could be partially caused by inadequate instructions on the way of opening this relatively uncommon type of blister. In the case of omeprazole, several brands are known to be packed in peel-off blisters, but examination of the package inserts showed that only two brands included instructions on how to open the peel-off blister. This might be true for other medication packed in peel-off blisters as well. Manufacturers are therefore advised to always include instructions on the correct removal of medicines from peel-off blisters in the package leaflet. Furthermore, pharmacy employees should inform patients on the use of the relatively uncommon peel-off blister pack. When problems remain, some patients might benefit from switching to a different packaging type.

Patients often mentioned transferring all the medicines from a blister to a bottle/container themselves. This could impair the quality of the medication. Omeprazole, for instance, is a sensitive product; both the capsules and the gastro-resistant pellets inside are sensitive to degradation by moisture, and for this reason omeprazole is packed in aluminium-based blisters, or in bottles or containers containing a desiccant. Removal of omeprazole from the original packaging may introduce moisture-induced changes to the physicochemical properties of the medicinal product, which could consequently affect its bioavailability by reduced dissolution of omeprazole from the pellets.[11, 12] For safety and product quality reasons it is generally preferred that pharmacists advise patients whether or not the medicine can be removed from its original packaging for a long period of time.

Some patients did not report any management strategy for opening their packaging. Although this could mean that patients were still able to extract the medicine (just not in a way they considered efficient), it could also suggest that these patients were unable to take their medication. This emphasises the importance of attention to packaging at the pharmacy counter, by demonstrating a method for opening the package or by asking patients about their experiences.

Although we focused on omeprazole in our study for practical reasons (i.e. it is widely prescribed, and available in different packaging forms) we expect our results to reflect patient experiences with similar packaging systems for other medicines. Manufacturers need to balance product quality against the usability of the packaging system, which can be equally detrimental to therapy effectiveness if it causes (partial) non-adherence. Problems experienced with removing medicines from their container systems are related to several technical design aspects of pharmaceutical products, such as the push-through force for blister materials, the hardness or breakability of tablets and capsules or the ease of opening child-resistant or tamper-evident containers. It is therefore advised that during the development stage of medicinal products, attention is paid to those aspects of packaging design that affect the ease of opening and the subsequent removal of the medicinal product from its packaging.

The suitability of packaging materials could, for instance, be demonstrated by testing the usability of packaging systems with a panel that is representative of the older population.

Conclusions

This research indicates that there is a need for more patient friendly packaging material and patient information on how to use relatively uncommon packaging systems. Furthermore, pharmacy staff should pay more attention to identifying the practical problems that people experience with the daily use of their medicines, and offer solutions to overcome these problems. This will contribute to safe and effective use of medicines.

References

1. van Geffen EC, Meuwese E, Philbert D, Bouvy ML. Problems with medicine packages: Experiences reported to a dutch medicine reporting system. Ann Pharmacother. 2010;44(6):1104-9
2. Keram S, Williams ME. Quantifying the ease or difficulty older persons experience in opening medication containers. J Am Geriatr Soc. 1988;36(3):198-201
3. Beckman A, Bernsten C, Parker MG, Thorslund M, Fastbom J. The difficulty of opening medicine containers in old age: A population-based study. Pharm World Sci. 2005;27(5):393-8
4. Verheggen-Laming BN, Phiferons H, Mulder EF, van der Meij NT, van Harten RP, Dijkmans BA. Comparison of packages for suppositories by patients with rheumatoid arthritis. Scand J Rheumatol. 1988;17(3):161-5
5. Kairuz T, Bye L, Birdsall R, Deng T, Man L, Ross A*, et al.* Identifying compliance issues with prescription medicines among older people: A pilot study. Drugs Aging. 2008;25(2):153-62
6. MacLaughlin EJ, Raehl CL, Treadway AK, Sterling TL, Zoller DP, Bond CA. Assessing medication adherence in the elderly: Which tools to use in clinical practice? Drugs Aging. 2005;22(3):231-55
7. Hughes CM. Medication non-adherence in the elderly: How big is the problem? Drugs Aging. 2004;21(12):793-811
8. Gipdatabase. Www.Gipdatabank.Nl [Internet]. [cited 30 November 2012].
9. SFK. One out of every three elderly people takes proton pump inhibitors. Pharm Weekblad. 2008;47(13)
10. Muhlfeld L, Langguth P, Hausler H, Hagels H. Influence of blister package design on usability among older adults. Int J Clin Pharm. 2012;34(4):553-60
11. Palummo M, Cingolani A, Dall L, Volonte MG. Stability of capsules containing omeprazole in enteric coated pellets. Boll Chim Farm. 2000;139(3):124-8
12. Storpirtis S, Rodrigues D. In vitro evaluation of dissolution properties and degradation products of omeprazole in enteric-coated pellets. Drug Dev Ind Pharm. 1998;24(11):1101-7

2.2

Chapter 2.2

Practical problems with medication use that older people experience: a qualitative study

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Abstract

Objective

To identify the practical problems that older people experience with the daily use of their medicines and their management strategies to address these problems and to determine the potential clinical relevance thereof.

Design

Qualitative study with semi-structured face-to-face interviews.

Setting

A community pharmacy and a geriatric outpatient ward.

Participants

Community-dwelling people aged 70 and older (N = 59).

Measurements

Participants were interviewed at home. Two researchers coded the reported problems and management strategies independently according to a coding scheme. An expert panel classified the potential clinical relevance of every identified practical problem and associated management strategy using a 3-point scale.

Results

Two hundred eleven practical problems and 184 management strategies were identified. Ninety-five percent of the participants experienced one or more practical problems with the use of their medicines: problems reading and understanding the instructions for use, handling the outer packaging, handling the immediate packaging, completing preparation before use, and taking the medicine. For 10 participants, at least one of their problems, in combination with the applied management strategy, had potential clinical consequences and 11 cases (5% of the problems) had the potential to cause moderate or severe clinical deterioration.

Conclusion

Older people experience a number of practical problems using their medicines, and their strategies to manage these problems are sometimes suboptimal. These problems can lead to incorrect medication use with clinically relevant consequences. The findings pose a challenge for healthcare professionals, drug developers, and regulators to diminish these problems.

Introduction

The correct and timely use of medication determines its therapeutic effect, yet a number of steps are involved in taking medicines as recommended, such as reading and understanding the user information, opening and removing the medicine from the outer and inner packaging, any preparation before use, and taking the medicine. Physical constraints such as impaired vision, poor handgrip strength, loss of fine motor skills, and dysphagia can hamper these activities, and these constraints increase as people age.[1-9] Strategies to manage these practical problems, or a lack thereof, could negatively affect the correct and timely use of medicines (e.g., when doses are omitted because assistance is needed to open a container).[1, 10]

Knowledge of the practical problems that older people experience with the use of their medicines and of strategies for addressing these problems is limited. Studies have investigated one or several specific problems with the use of medicines[3, 4, 6, 11-14], but to the knowledge of the authors of the current study, no study has investigated the problems that could occur during the complete sequence of steps that individuals must undertake with the use of their own medicines. Furthermore, only a few studies have addressed the potential clinical consequences of practical problems using applied management strategies.[1, 15, 16]

This study aimed to identify the practical problems that older people experience with the daily use of their medicines and their management strategies to address these problems and to determine the potential clinical relevance thereof.

Methods

Study design and setting

This was a qualitative study using semi-structured interviews with older people. Participants were recruited from a community pharmacy and the geriatric outpatient ward of the University Medical Centre Utrecht (UMCU), both in the Netherlands. Participants were eligible if they were community dwelling, aged 70 and older, and using at least three different oral prescription medicines daily. Individuals were excluded if a professional or family caregiver managed their medication entirely, or if the medication was delivered in multidose dispensing systems.

Recruitment of participants continued until data saturation was achieved. Saturation was defined as the absence of new practical problems and management strategies in five consecutive interviews.

This study was not subject to the Medical Research Involving Human Subjects Act. The UPPER institutional review board reviewed the study, which was conducted in compliance with its requirements (http://www.uu.nl/vkc/ upper).

Data collection

Practical problems with medication use were defined as problems related to the presentation and formulation of a medicine and included labeling, information leaflet, material and type of outer and inner packaging, administration device, colour, shape, size, taste, surface texture, and any break mark on a medicine. Participants were interviewed at home. Before the start of the interview, participants were asked to collect all medicines, which were verified with the dispensing record that their community pharmacy provided with their consent. Field notes that the researchers made during the interview were verified with the participants at the end of the interview.

Data management and analysis

All interviews were recorded and transcribed verbatim. The transcripts were imported in ATLAS.ti (version 7.0; Scientific Software Development GmbH, Berlin, Germany). The combination of voice recording and field notes ensured the reliability and validity of the transcribed data. Two authors (KN, EB) coded independently. Disagreements in coding were discussed until consensus was reached. Another researcher (MLB, ACGE, or PAFJ) was consulted if consensus was not reached.

An expert panel (MLB, ACGE, PAFJ) independently classified the potential clinical relevance of every identified practical problem and associated management strategy on a 3-point scale.[17] Class 1 relevance was defined as unlikely to cause discomfort or clinical deterioration, Class 2 as having the potential to cause moderate discomfort or clinical deterioration, and Class 3 as having the potential to result in severe discomfort or clinical deterioration. Disagreements in classification were discussed within the expert panel until consensus was reached.

Results

Fifty-nine people (mean age 78.4, range 70–92) participated in this study; 38 (64.4%) were women, and 30 (50.8%) were living alone. On average, participants used 6.9 prescribed oral medicines (range 3–12). Two hundred eleven problems were reported, ranging from no problems in three participants to 14 problems in one participant, and 184 management strategies were reported for these problems.

Although 94.8% of the problems were unlikely to result in discomfort or clinical deterioration (Class 1), 5.2% (11 problems) were considered to have the potential to cause discomfort or clinical deterioration (Class 2 or 3). Table 1 shows the reported problems and management strategies. A taxonomy of the identified practical problems is presented in Figure 1.

Reading and understanding instructions for use

Thirty-seven participants reported problems with reading and understanding the instructions for use. Twenty-two participants were worried about adverse events reported in the information leaflet; as a result, three reduced the dose or did not take the medicine at all. For one participant who regularly omitted doses of pantoprazole, this was considered to have the potential to cause discomfort or clinical deterioration because of the risk of gastric bleeding (Table 2).

I decided to restrict myself to one every 2 days. This is because I consider it harmful rubbish. You can expect all kinds of problems, and the side effects are gigantic. Maybe you think I shouldn't get upset about this, but I wish I hadn't read the instruction leaflet.
(Male, 80 years, pantoprazole 20 mg)

Handling outer packaging

Nine of the problems with handling the outer packaging concerned opening. The use of scissors or a knife was reported to overcome this problem in five cases.

At a certain moment, the box became more difficult to open. Both ends were stuck down. This wasn't previously the case, so why are they stuck down now? Is this to make life more difficult? You just have to scratch it open with your fingernails. This is actually quite difficult.
(Male, 71 years, atorvastatin 20 mg)

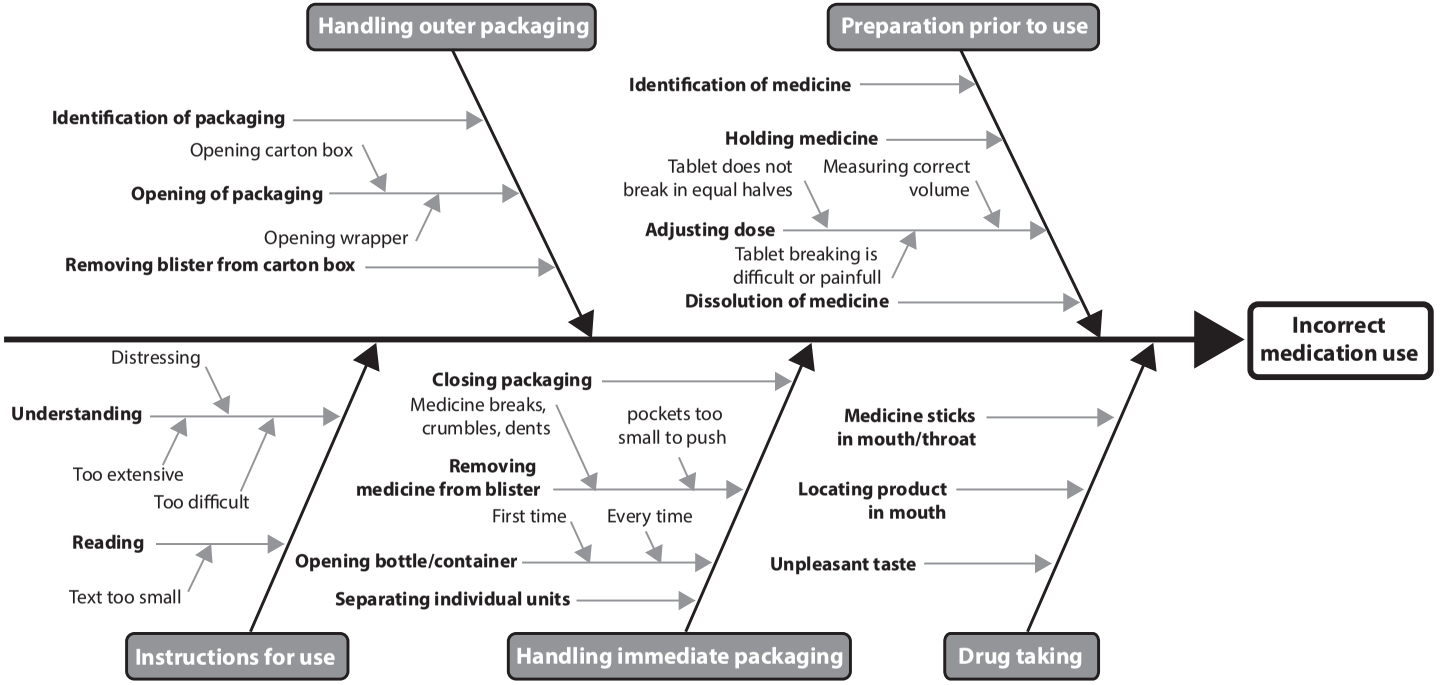
Difficulties with the identification of medicines were reported (n = 3). Two participants wrote the therapeutic indication on the carton to avoid confusing boxes that looked alike. Problems with the handling of the outer packaging were considered not to have clinical consequences.

Table 1 Practical problems and related management strategies as reported by 59 participants

Practical Problem	Management Strategy
Reading and Understanding Instructions for Use (53 total reported, by 37 participants)	
Text too small (12)	No solution/Not reading package insert (regularly) (6), Use of magnifying glass (5), Use of extra light (1)
Information is too difficult (5)	No solution/Not reading package insert (regularly) (4), Read information on packaging (1)
Information is too extensive (12)	No solution/Not reading package insert (regularly) (12)
Information on adverse events is distressing (24)	Not reading PIL (regularly) (19), No solution (3), Using no or lower dose (3)
Handling of Outer Packaging (19 total reported, by 17 participants)	
Identification of product (3)	Writing on packaging (2), No solution (1)
Opening of packaging:	
- carton box (6)	Other way of opening (3), Using sharp equipment (3)
- wrapper around blister (3)	Using sharp equipment (2), No solution (1)
Removing blister from carton box (7)	Remove package insert (7)
Handling of Immediate Packaging (73 total reported, by 38 participants)	
Separating individual units (9) (sachets, vials, or blister cups)	Using sharp equipment (5), No solution (2), using nails (1)
Opening of packaging:	
- for the first time (13)	Assistance (6), Using sharp equipment (3), Using auxiliary aid (2), No solution (2)
- every time (7)	Not closing properly (4), Using other packaging (2), Assistance (1), Using sharp equipment (1), No solution (1), Push/twist with palm of hand (1)
Removing medicine from:	
- bottle (1)	Using other packaging (1)
- blister (42)	Using sharp equipment (8), No solution (6), Using nails (1), Change to packaging (1)

- *Medicine dents, opens, breaks or crumbles (15)*	Administration of pieces (9), Take another dosage (2), Using nails (2), No solution (1)
- *Tearline tears instead of blister opening (4)*	No solution (4)
- *Pockets too small to push (7)*	Using nails (to push on pocket/open lidding foil) (6), Remove two tablets at once (1)
- *Pockets too large to localise product (1)*	Using nails (1)
Closing packaging (1)	No solution (1)
Preparation Prior to Use (38 total reported, by 23 participants)	
Identification of medicine (10)	Store separate from look-a-like medicine (5), writing on packaging (2), reading embossment (1)
Holding medicine (12)	No solution (12)
Tablet breaking (9)	
- Difficult/painful (5)	No solution (3), assistance (1), using tablet splitter (1)
- No equal halves/crumbles (4)	Take another (2), administration of pieces (1), using tablet splitter (1)
Measuring correct volume (1)	No solution (1)
Dissolution/disintegration of medicine (6)	No solution (6)
Drug taking (28 total reported, by 17 participants)	
Medicine sticks in throat/mouth (17)	Taking additional water or food (12), Breaking tablet (2), No solution (2), Taking the product before the other products (1)
Locating product in mouth (1)	No solution (1)
Unpleasant taste (10)	Drug taking with food or additional water (5), Taking the product before the other products (2), No solution (2), Swallowing complete tablet instead of chewing (1)

Figure 1. Ishikawa-diagram outlining practical causes of incorrect medication use per sequential step of the medication use process



Handling immediate packaging

Forty-three of the problems with the handling of the immediate packaging concerned the removal of medicines, 14 of which were related to tablets breaking or crumbling when removing them from a blister pack. Nine participants administered the resulting fractions. In three cases, the unintended breaking of a tablet was considered to have the potential to cause discomfort or clinical deterioration (Table 2). For example, one participant who used glyburide risked fluctuations in blood glucose by taking tablet parts instead of a whole tablet.

It often breaks when I'm pressing it out. I always have to look to see where the other half of the tablet is. I often find it lying somewhere else. I try to be careful when I am doing it so that it doesn't break in half, and sometimes it works, and sometimes it doesn't. I consume the tablet parts as a whole, so to say.
(Male, 71 years, glyburide 5 mg)

Other problems with the handling of the immediate packaging concerned difficulty with first-time opening of containers (n = 13) and with repeatedly opening the containers (n = 7). Reported ways to overcome these problems were to ask help of a partner or caregiver (n = 7) and to use a jar opener (n = 2) or a knife (n = 4).

Preparation before use

Thirty-eight participants reported problems when preparing their medicine. Eleven participants reported difficulties identifying medicines after removal of their packaging. One participant experienced difficulty distinguishing two different strengths of levodopa/benserazide tablets because of similarity in appearance. This was considered to have the potential to cause discomfort or clinical deterioration because accurate intake is important to control Parkinson's disease (Table 2).

So, if I have this [participant holds up the bottle of levodopa/benserazide], but then it is bigger than this I believe. I find it difficult to tell. When you put them next to each other, it's easier to see. I should have been told this when I was given the instructions. So, at first I was taking them randomly because I couldn't see what I was doing.
(Male, 74 years, levodopa/benserazide 100/25 mg and 200/50 mg)

Furthermore, breaking of tablets was reported as difficult or painful (n = 5) or as resulting in unequal parts or crumbles (n = 4). This was considered to have the potential to cause discomfort or clinical deterioration in one participant who was taking phenprocoumon because of the narrow therapeutic index (Table 2).

I have to take half a tablet. There is a nice groove. I have good fingernails that fit nicely into the groove. Nine times out of ten I break the tablet in two, and one-half is so big and the other half so big. So, not the same amount every day.
(Male, 73 years, phenprocoumon 3 mg)

Drug taking
Twenty-eight problems related to the taking of medicines were reported. One of these problems concerned lodging of the medicine in the mouth or throat (n = 17). For one participant, who used alendronic acid, this was considered to have the potential to cause discomfort or clinical deterioration due to the possible development of esophageal ulceration (Table 2).

It's just that I think the tablet is too big to swallow. I drink a lot of warm water. Then it doesn't get stuck. And you are not allowed to break the tablet, so I take it with a lot of water, warm or hot water.
(Female, 83 years, alendronic acid 70 mg)

Problems with the flavour of medicines were reported (n = 10). One participant reported swallowing medicines with yogurt to mask the taste. One of these medicines was ferrous fumarate. This was considered to have the potential to cause discomfort or clinical deterioration by decreasing absorption of iron (Table 2):

I start in the morning with seven, and that is an awful lot. Because sometimes you really hate to chew on them. I say chew because they are quite difficult to consume properly. Nowadays I take those that don't go down so well with a little yogurt. I do this with the large one, but also with the small ones, because one of them is bitter. And this is usually quite unpleasant.
(Female, 83 years, ferrous fumarate 200 mg)

Table 2 Details of the cases assigned as Class 3 or Class 2 relevance

Practical Problem	Management Strategy	Case	Clinical relevance*
Reading and understanding instructions for use			
Worried by the side effects listed in the package insert (n=1)	Participant took the tablets every other day instead of once every day as prescribed	Pantoprazole 20 mg	Class 3
Handling immediate packaging			
The tablet breaks or crumbles when the patient removes it from the blister (n=3)	Participant administered the resulting pieces and crumbles	Enalapril 20 mg, furosemide 40 mg, glyburide 5 mg	Class 2
Preparation prior to use			
Difficulty with the identification of the medicine (n=1)	No strategy reported	Pantoprazole 20 mg	Class 2
Difficulty filling measurement cup with correct volume (n=1)	No strategy reported	Promethazine 1 mg/ml	Class 2
Difficulty with the identification of the different strengths (n=1)	Participant wrote indication on packaging	Levodopa/benserazide 200/50 mg & 100/25 mg	Class 3
Tablet does not break into equal halves and/or crumbles (n=2)	Participant administered the unequal halves	Phenprocoumon 3 mg	Class 3
Drug taking			
Lodging of tablet in mouth/throat when swallowing (n=1)	Participant swallowed the tablet with an additional amount of water	Alendronic acid 70 mg	Class 2
Tablet has an unpleasant flavour (n=1)	Participant swallowed the tablet with yoghurt	Ferrous fumarate 200 mg	Class 3

* Potential clinical relevance:
- Class 2: potential to result in moderate discomfort or clinical deterioration.
- Class 3: potential to result in severe discomfort or clinical deterioration.

Discussion

Ninety-five percent of participants experienced one or more practical problems with using their oral prescription medicines. Most participants developed strategies to resolve the practical problems they experienced. Although several participants experienced the same problems, the potential clinical implications varied for each individual participant because they used different medicines and different strategies to resolve the problem. For 10 participants (17%), at least one of their problems was considered to have the potential to cause clinical deterioration, adding up to a total of 11 potentially clinically relevant situations. Ninety-five percent of the problems were considered not to be clinically meaningful, but even so they caused inconvenience and should be resolved. Moreover, if a person experiences problems with multiple medicines, the likelihood increases that these problems will adversely affect health.[18] This is especially likely in frail, more physically restricted individuals with complex medication regimens. Furthermore, the problems found in this study were related to oral medication. People may also have problems administering non-oral dosage forms, such as eye drops[19, 20], sublingual sprays[13], and inhalers[10].

Strengths and limitations

This study evaluated the complete sequence of handling activities after dispensing. Through this approach, previously unreported practical problems were identified, such as difficulties opening the box; separating linked sachets, vials, or blister cups; holding medicines; and dissolving powders. The strategies participants used to manage these problems and the potential clinical consequences of these strategies were systematically investigated. Previous studies did not investigate participants' management strategies or focused on medication adherence without discussing clinical consequences.[1, 16, 21] There is the risk of reporting bias and recall bias. Also, rare practical problems might have been missed, but because participants were recruited from two settings, and the level of saturation was strict, the study gives a good overview of commonly experienced problems.

Implications for drug developers and practice

To enhance the safety and efficacy of medicines for use in older people, the practical problems that older people may encounter with taking medicines should be taken into consideration during the development, evaluation, prescription, and dispensing of medicines. This is especially relevant for unforgiving medicines (medicines for which a dose other than the prescribed dose can have direct safety implications).[22] The pharmaceutical industry can address the needs and concerns of older people during the development of medicines. Currently, information leaflets appear to miss their main aim—at least for older adults—of providing relevant information on the use of the medicine by containing

too much, too difficult, and too distressing information. The design of medicine packaging needs to take into consideration the decreased handgrip strength and manual dexterity of older people. Developing tamper-evident and child-resistant closures that remain accessible for older people is a challenge. The usability of pill bottles and containers and of blister packs could be improved. Furthermore, the visual identification of medicines should be addressed during pharmaceutical development to decrease the possibility of people confusing medicines or different strengths. Preferably, medicines should be available in appropriate dosages so that the need for splitting pills is kept to a minimum. When splitting pills is unavoidable, it should be ensured that this results in equal parts in a sufficiently easy way. The ease of holding and swallowing the medicine should also be taken into account during development, because older people have poorer fine motor skills and experience swallowing difficulties more often than younger adults.[23] Thought should be given to addressing the suitability of medicines for use by older people during the evaluation of medicines by regulatory agencies. In addition to the industry and regulators, healthcare providers can address potential practical problems with medication use when prescribing and dispensing medicines to older people. Because people rarely report practical problems spontaneously to physicians or pharmacists, pharmacists should proactively inquire about practical problems.[24] They can select a medicine with the most-appropriate presentation and formulation for the individual, such as a dosage that does not need to be divided, a form that causes fewer swallowing difficulties, or use of more user-friendly packaging.

Conclusion

Older people experience a broad range of practical problems with the use of their medicines. Incorrect medication use caused by these problems may have clinical consequences. All stakeholders concerned with the development, evaluation, prescription, and dispensing of medicines can and should help diminish the practical problems that older people experience.

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References

1. Kairuz T, Bye L, Birdsall R, Deng T, Man L, Ross A*, et al.* Identifying compliance issues with prescription medicines among older people: A pilot study. Drugs Aging. 2008;25(2):153-62
2. Kelly J, D'Cruz G, Wright D. Patients with dysphagia: Experiences of taking medication. J Adv Nurs. 2010;66(1):82-91
3. Ruscin JM, Semla TP. Assessment of medication management skills in older outpatients. Ann Pharmacother. 1996;30(10):1083-8
4. Nikolaus T, Kruse W, Bach M, Specht-Leible N, Oster P, Schlierf G. Elderly patients' problems with medication. An in-hospital and follow-up study. Eur J Clin Pharmacol. 1996;49(4):255-9
5. Stegemann S, Ecker F, Maio M, Kraahs P, Wohlfart R, Breitkreutz J*, et al.* Geriatric drug therapy: Neglecting the inevitable majority. Ageing Res Rev. 2010;9(4):384-98
6. Atkin PA, Finnegan TP, Ogle SJ, Shenfield GM. Functional ability of patients to manage medication packaging: A survey of geriatric inpatients. Age Ageing. 1994;23(2):113-6
7. Isaac LM, Tamblyn RM. Compliance and cognitive function: A methodological approach to measuring unintentional errors in medication compliance in the elderly. Mcgill-calgary drug research team. Gerontologist. 1993;33(6):772-81
8. Ostrom JR, Hammarlund ER, Christensen DB, Plein JB, Kethley AJ. Medication usage in an elderly population. Med Care. 1985;23(2):157-64
9. Tordoff JM, Bagge ML, Gray AR, Campbell AJ, Norris PT. Medicine-taking practices in community-dwelling people aged > or =75 years in new zealand. Age Ageing. 2010;39(5):574-80
10. Thwaites JH. Practical aspects of drug treatment in elderly patients with mobility problems. Drugs Aging. 1999;14(2):105-14
11. Philbert D, Notenboom K, Bouvy ML, van Geffen EC. Problems experienced by older people when opening medicine packaging. Int J Pharm Pract. 2014;22(3):200-4
12. Barends DM, Groot DW, van der Steen JC, de Kaste D, Frijlink HW. Results of a market surveillance study in the netherlands on break-mark tablets. Pharmeur Sci Notes. 2006;2006(2):1-7
13. Tordoff J, Simonsen K, Thomson WM, Norris PT. "It's just routine." A qualitative study of medicine-taking amongst older people in new zealand. Pharm World Sci. 2010;32(2):154-61
14. van Geffen EC, Meuwese E, Philbert D, Bouvy ML. Problems with medicine packages: Experiences reported to a dutch medicine reporting system. Ann Pharmacother. 2010;44(6):1104-9
15. Denneboom W, Dautzenberg MG, Grol R, De Smet PA. User-related pharmaceutical care problems and factors affecting them: The importance of clinical relevance. J Clin Pharm Ther. 2005;30(3):215-23
16. Schiele JT, Quinzler R, Klimm HD, Pruszydlo MG, Haefeli WE. Difficulties swallowing solid oral dosage forms in a general practice population: Prevalence, causes, and relationship to dosage forms. Eur J Clin Pharmacol. 2013;69(4):937-48
17. Cornish PL, Knowles SR, Marchesano R, Tam V, Shadowitz S, Juurlink DN*, et al.* Unintended medication discrepancies at the time of hospital admission. Arch Intern Med. 2005;165(4):424-9
18. Evans DC, Cook CH, Christy JM, Murphy CV, Gerlach AT, Eiferman D*, et al.* Comorbidity-polypharmacy scoring facilitates outcome prediction in older trauma patients. J Am Geriatr Soc. 2012;60(8):1465-70
19. Blenkiron P. The elderly and their medication: Understanding and compliance in a family practice. Postgrad Med J. 1996;72:671-6
20. Dietlein TS, Jordan JF, Luke C, Schild A, Dinslage S, Krieglstein GK. Self-application of single-use eyedrop containers in an elderly population: Comparisons with standard eyedrop bottle and with younger patients. Acta Ophthalmol. 2008;86(8):856-9
21. Orwig D, Brandt N, Gruber-Baldini AL. Medication management assessment for older adults in the community. Gerontologist. 2006;46(5):661-8
22. Urquhart J. Patient non-compliance with drug regimens: Measurement, clinical correlates, economic impact. Eur Heart J. 1996;17 Suppl A:8-15
23. Stegemann S. Challenges and opportunities in the design of age-appropriate drug products. Z Gerontol Geriatr. 2012;45(6):479-84
24. Philbert D, Notenboom K, Koster ES, Fietjé EH, Van Geffen EC, Bouvy ML. Pharmacy technicians' attention to problems with opening medicine packaging J Pharm Technol. 2014;30(1):3-7

Chapter 3

The suitability of the design of medicines for use by older people

3.1

Chapter 3.1

Relationship between age and the ability to break scored tablets

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Abstract

Background

Practical problems with the use of medicines, such as difficulties with breaking tablets, are an often overlooked cause for non-adherence. Tablets frequently break in uneven parts and loss of product can occur due to crumbling and powdering. Health characteristics such as the presence of peripheral neuropathy, decreased grip strength and manual dexterity, can affect a patient's ability to break tablets. As these impairments are associated with ageing and age-related diseases such as Parkinson's disease and arthritis, difficulties with breaking tablets could be more prevalent among older adults. The objective of this study was to investigate the relationship between age and the ability to break scored tablets.

Methods

A comparative study design was chosen. Thirty-six older adults and thirty-six young adults were systematically observed with breaking scored tablets. Twelve different tablets were included. All participants were asked to break each tablet by three techniques: in between the fingers with the use of nails, in between the fingers without the use of nails and pushing the tablet downward with one finger on a solid surface. It was established whether a tablet was broken or not, and if broken, whether the tablet was broken accurately or not.

Results

The older adults experienced more difficulties to break tablets compared to the young adults. On average, the older persons broke 38.1% of the tablets, of which 71.0% was broken accurately. The young adults broke 78.2% of the tablets, of which 77.4% was broken accurately. Further analysis by mixed effects logistic regression revealed that age was associated with the ability to break tablets, but not with the accuracy of breaking.

Conclusions

Breaking scored tablets by hand is less successful in an elderly population compared to a group of young adults. Health care providers should be aware that tablet breaking is not appropriate for all patients and for all drugs. In case tablet breaking is unavoidable, a patient's ability to break tablets should be assessed by health care providers and instructions on the appropriate method of breaking should be provided.

Introduction

Pharmaceutical care becomes more complicated with advanced age because the characteristics and health problems of older adults people are different and often more complex than those of young adults. Current incentives to optimise pharmacotherapy in the geriatric population include reducing inappropriate prescribing and improving medication adherence.[1-5] Practical problems that hinder older patients to use their medicines correctly, such as difficulties opening packaging, swallowing medicines or breaking tablets, are an often overlooked cause for non-adherence. However, these problems can lead to incorrect use of medicines with clinically relevant consequences.[6]

Several studies have shown that patients experience breaking of scored tablets a difficult or painful task.[6-9] Tablets frequently break in uneven parts and loss of product can occur due to crumbling and powdering, which impedes the accuracy of dosing.[10-15] At the same time, tablet breaking is common practice, with an estimated frequency in primary care at 24%-31%.[16, 17] Characteristics of a tablet, such as size, shape, hardness, and one- or two-sided presence of the score line, have an impact on how easy a tablet can be broken.[10, 18, 19] Furthermore, the method of breaking can affect the ease and accuracy of breaking.[13, 20] Health characteristics such as the presence of peripheral neuropathy, decreased grip strength and manual dexterity, or vision problems can influence a patient's ability to break tablets. As these impairments are associated with ageing and age-related diseases such as Parkinson's disease and arthritis, difficulties with breaking tablets could be more prevalent among older adults compared to young adults. Concurrently, elderly people are more often in need of scored tablets, as they often require a lower dose strength compared to young adults. These lower strengths are not always available.[16]

Little is known about the ability of older adults to break scored tablets manually. Findings are contradictory, and previous studies evaluated only one or two tablets, allowed the use of splitters or did not address breaking methodology at all.[12, 21] Therefore, the objectives of this study were to investigate the relationship between age and the ability to break a large sample of scored tablets by three manual techniques for breaking tablets.

Materials and methods

Study design

A comparative study design was chosen. Thirty-six older adults and 36 young adults were systematically observed with breaking twelve different, scored tablets, each tablet by three common techniques for breaking tablets by hand.

Participants

The older people were recruited in five residential homes for elderly in the area of Utrecht, the Netherlands. People were eligible if they were aged 65 and older and managed their own medication. Exclusion criteria were dementia, blindness and impaired use of hands and/or fingers. These criteria derive from a test procedure to assess the ability of older people to break scored tablets, which was developed in a previous study.[22] Employees of the residential homes approached eligible people and explained the purpose of the study. When interested, they were given an information letter that included more detailed information about the study. After a week, approached people were asked whether they wanted to participate in the study. One person was excluded by the researchers at the start of the study because of temporarily impaired use of hands. Four individuals dropped out during the first day of the study: two due to loss of interest, one because of too much pain in the shoulder during the breaking of the tablets, and the fourth person found the study too intensive. Excluded and dropped out individuals were replaced.

The young adults were recruited among Master students from the School of Pharmacy at Utrecht University, the Netherlands. Participation of the young adults was on voluntary basis as part of a study course. All 36 approached young adults agreed to participate and finalised the study.

The study was not subject to The Medical Research Involving Human Subjects Act (WMO). The study was conducted in compliance with the requirements of the UPPER institutional review board (http://www.uu.nl/vkc/upper). For this type of study, informed consent is not required in the Netherlands.

Tablets

Twelve commercially available scored tablets were selected for this study: four different active pharmaceutical ingredients, and three different brands of each: bisoprolol 5 mg, citalopram 20 mg, enalapril 5 mg and paroxetine 20 mg (coded A1-3, B1-3, C1-3 and D1-3, respectively). The criteria for selection of the tablets were presence of a score line intended for subdivision into equal doses and common use in the geriatric population. At least one of the brands of each active pharmaceutical ingredient had a pressure sensitive score line. The tablets differed in size, shape, and score-line characteristics (Figure 3).

Sample size

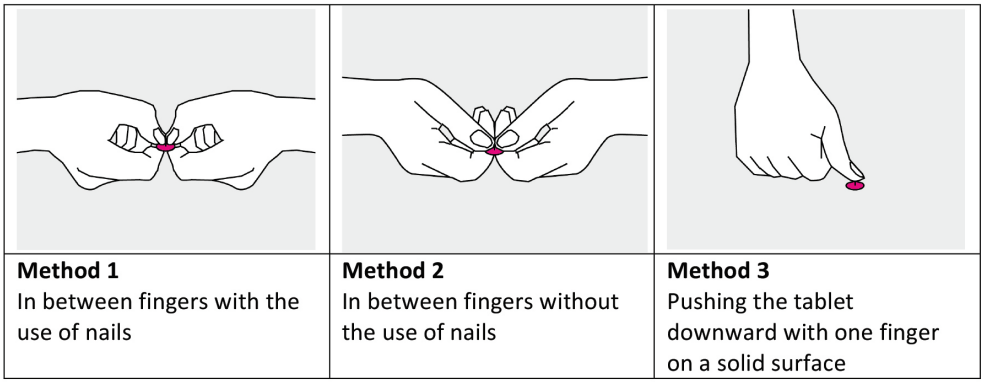
Sample size was calculated based upon data generated by a previous study on the ability of older adults to break tablets. It was found that older people were able to break 74% of the tablets, taking the multiple measurements within each participant into account.[19, 22] With

a type one error (α) for a one-sided test of 0.05 and a power of 80%, it was found that 10 participants were needed in each of the two age groups to demonstrate a difference of 15% in the ability to break tablets, again taking the multiple measurements within each participant into account. As we aimed to investigate several potential determinants, we decided to include a convenience sample of 36 participants per age group.

Data collection and measures

The twelve tablets were broken by each participant, each tablet by three common techniques for breaking tablets by hand: breaking in between the fingers with the use of nails, breaking in between the fingers without the use of nails and pushing the tablet downward with one finger on a solid surface (Figure 1). The participants received a written and a verbal explanation of these three techniques. Tablet breaking was spread over two days for each participant and a three-hour break was implemented halfway on each day. The tablets were presented to the participants in a random order to minimise the possible effects of "training in breaking" and "getting tired after some acts of breaking". Participants' age and sex, and experience with tablet breaking were collected.

Figure 1 The three methods used in the study for breaking scored tablets by hand



Method 1 In between fingers with the use of nails	**Method 2** In between fingers without the use of nails	**Method 3** Pushing the tablet downward with one finger on a solid surface

The primary outcome measures were the ability of the participants to break the tablets and the ability of the participants to break the tablets in equal halves, i.e. the accuracy of breaking. To determine the ability of breaking, it was established whether a tablet was broken or not. Tablets were scored as 'broken' regardless of the outcome of breaking, e.g. broken in two halves, in three of more fractions, crumbled or powdered upon breaking. The accuracy of breaking was determined for each broken tablet based upon the mass deviation of the obtained tablet parts from the theoretical halved weight of the parent tablet. A deviation of not more than 15.0% from the theoretical halved weight of the parent tablet was allowed.

This criterion was derived from the European Pharmacopeia.[23] Only tablets for which both halves complied with the criterion were scored as 'accurately broken'. When tablets broke into quarters, two quarters were combined and treated as halves. In case the quarters remained attached by the coating layer, the attached parts were considered as halves. In all other situations, e.g. when tablets were broken into three, five or more parts or completely crumbled upon breaking, the tablet was considered as exceeding the permitted deviation and scored as 'not accurately broken'.[24] Tablets were weighed individually and placed in a separate numbered and coded bag prior to breaking. After breaking, the resultant portions were returned to the same bag. The tablets and obtained tablet parts were weighed to the nearest 0.0001g (Mettler Toledo AT201 analytical balance).

Data analysis

Participants' characteristics are shown as mean and % (n). The aggregated results for the ability and accuracy of breaking for each age group are reported as relative frequencies. The proportions of broken tablets and accurately broken tablets were compared between groups by independent t-tests.

The relationship between age and the ability to break tablets, and the relationship between age and the ability to break tablets accurately was further evaluated by mixed-effects logistic regression modelling. Besides age, the fixed variables of interest were gender, method of breaking and tablet. Gender was included because the stronger grip strength of men can potentially influence their ability and accuracy of tablet breaking. Method of breaking and tablet characteristics are known to influence the ease and accuracy of tablet breaking. Because the data visualisation revealed a relation between type of score line and method of breaking, the interaction between tablet and method of breaking was added. Each model included a random intercept for the participants to account for within-participant correlation. Six models were fit to the data. Model 1 examined the relation between the ability or accuracy of breaking and age. Next, the explanatory variables were added to the first model. Model 2 included age and gender, Model 3 included age, gender and method of breaking, Model 4 included age, gender and tablet, Model 5 included age, gender, tablet and method of breaking, and Model 6 included age, gender, tablet, method of breaking and the interaction between tablet and method of breaking. The preferred model was selected using the Akaike information criterion (AIC). Effect estimates were reported as odds ratios (ORs), along with 95% confidence intervals (CIs). The discriminative ability of the model was assessed with the c-index (i.e. the area under the ROC curve). Statistical tests were two-sided, and significance was set at $P<0.05$. The t-tests were conducted using SPSS Statistics, version 22 (IBM SPSS), and R programming language version 3.2.2 was used for modelling (http://www.R-project.org/).

Results

The mean age of the 36 older participants was 84.2 years, and 69.4% were women. The mean age of the 36 young participants was 24.8 years, and 80.6% were women. Among the older participants, 22.2% was experienced with breaking tablets. None of the young participants was experienced with tablet breaking.
The participants' characteristics are presented in Table 1.

Table 1 Characteristics of the participants

Characteristics [a]	**Elderly people** (n = 36)	**Young adults** (n = 36)
Mean [SD] age, years	84.2 [6.8]	24.8 [1.8]
Women	25 (69.4%)	29 (80.1%)
Experienced with breaking tablets	8 (22.2%)	0 (0)

[a] *The information in this table is presented as (n)%, unless otherwise indicated.*

Each participant attempted to break a total of 36 tablets; twelve tablets by three different methods of breaking. Compared to the young participants, the ability of the older participants to break the tablets was significantly lower. On average, the older adults broke 38.1% of the 36 tablets and the young adults broke 78.2% of the 36 tablets (P<0.001). There was no statistically significant difference in the mean proportion of accurately broken tablets between the two age groups; the older adults broke on average 71.0% of the broken tablets accurately, whereas the young participants broke 77.4% of the broken tablets accurately (P=0.116). Although not our primary objective, we also compared the outcomes between the genders. On average, the proportion of tablets broken by male participants was significantly higher compared to the proportion broken by women (67.0% and 55.2%, respectively, P=0.035). This trend was observed in both age groups, although the difference was not significant among the young adults. Contrarily, the mean proportion of accurately broken tablets was lower for male participants compared to female participants (68.5 vs 76.1%; P=0.109). This difference was not significant.

There were no statistically significant differences in the proportion of tablets broken and the proportion of tablets broken accurately between older participants with and without experience in breaking tablets (38.5% vs 38.0%; P=0.951, and 69.3% vs 71.4%; P=0.813, respectively).

The results for the individual tablets, as visualised in Figure 2, showed that for each of the twelve tablets the proportion of tablets broken by the older participants was considerably

lower compared to the proportion broken by the young participants. For each individual tablet, no clear difference between the age groups was observed for the proportion of accurately broken tablets. Both the ability of breaking and the accuracy of breaking showed a high inter-tablet variability, which appeared similar between the two age groups. The proportion of tablets broken by the older participants ranged between 3.7% (tablet B1) and 74.1% (tablet C1), whereas the proportion of tablets broken by the young participants ranged between 27.8% (tablet B1) and 100% (tablet C1 and C2).

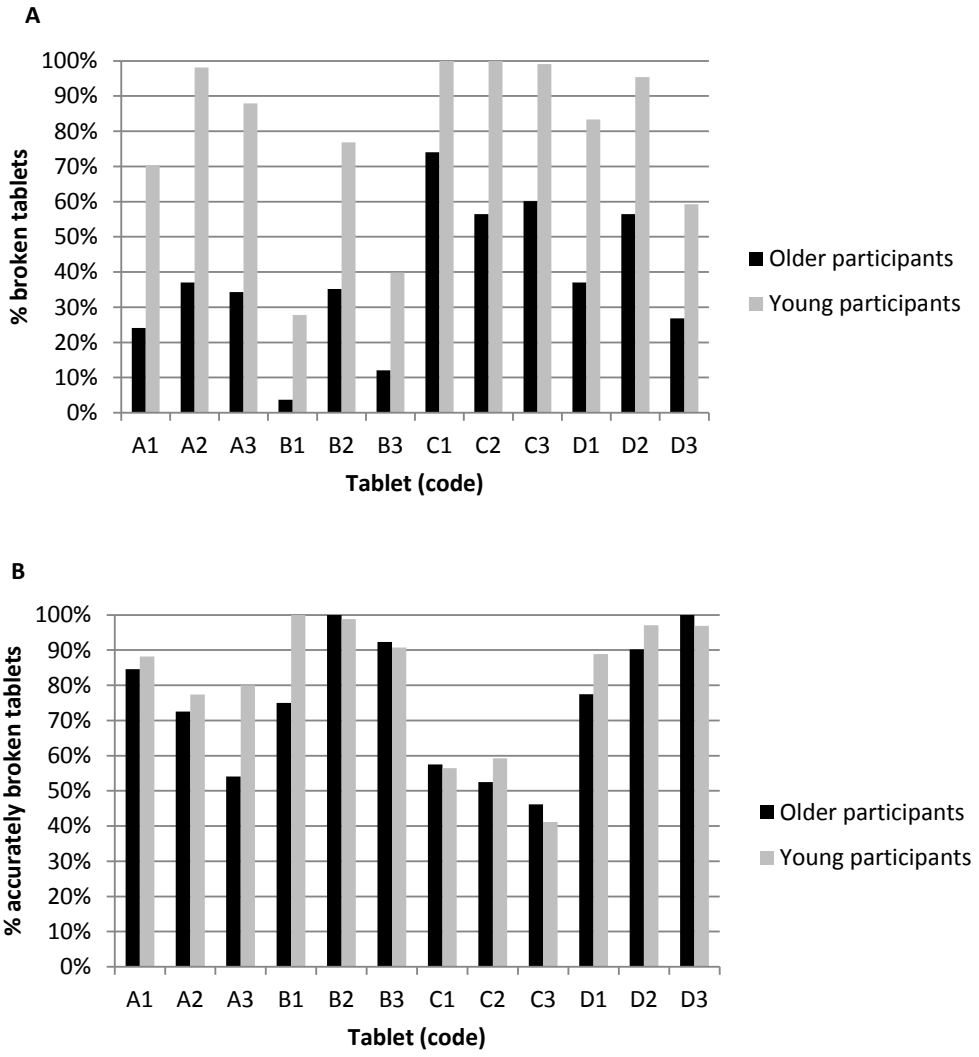
Figure 3 shows the ability of the older participants to break each of the twelve tablets by the three breaking techniques. The tablets with a pressure sensitive score line, i.e. tablets A1, B1, C1 and D1, were easier to break by pushing them downward on a hard flat surface. All other tablets were easier to break between the fingers, with the use of nails.

Table 2 Odds ratios (ORs) and model characteristics for the ability of breaking

	Age *Reference: Older participants*		**Gender** *Reference: Female participants*		**AIC**
Models	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**	
Model 1: Random effect for participant; fixed effect for age	7.23 (4.76;11.17)	<0.001	-	-	2920.5
Model 2: Model 1 + fixed effect for gender	7.93 (5.44;11.78)	<0.001	2.5 (1.62;3.85)	<0.001	2907.01
Model 3: Model 1 + fixed effects for gender and method of breaking	8.64 (5.83;13.05)	<0.001	2.59 (1.65;4.07)	<0.001	2823.41
Model 4: Model 1 + fixed effects for gender and tablet	19.38 (11.31;34.12)	<0.001	3.59 (1.96;6.57)	<0.001	2213.05
Model 5: Model 1 + fixed effects for gender, method of breaking and tablet	24.22 (13.56;44.76)	<0.001	3.95 (2.06;7.57)	<0.001	2090.54
Model 6: Model 5 + interaction between method of breaking and tablet	50.56 (25.02;108.03)	<0.001	4.99 (2.28;10.9)	<0.001	1809.76

CI = confidence interval; OR = odds ratio; AIC = aikake information criterion.

Figure 2 The results for ability and accuracy of breaking, for tablets A1-D3 individually



The percentage of tablets broken by the older and young participants **(A)**, and the percentage of accurately broken tablets, of those that were broken **(B)**.

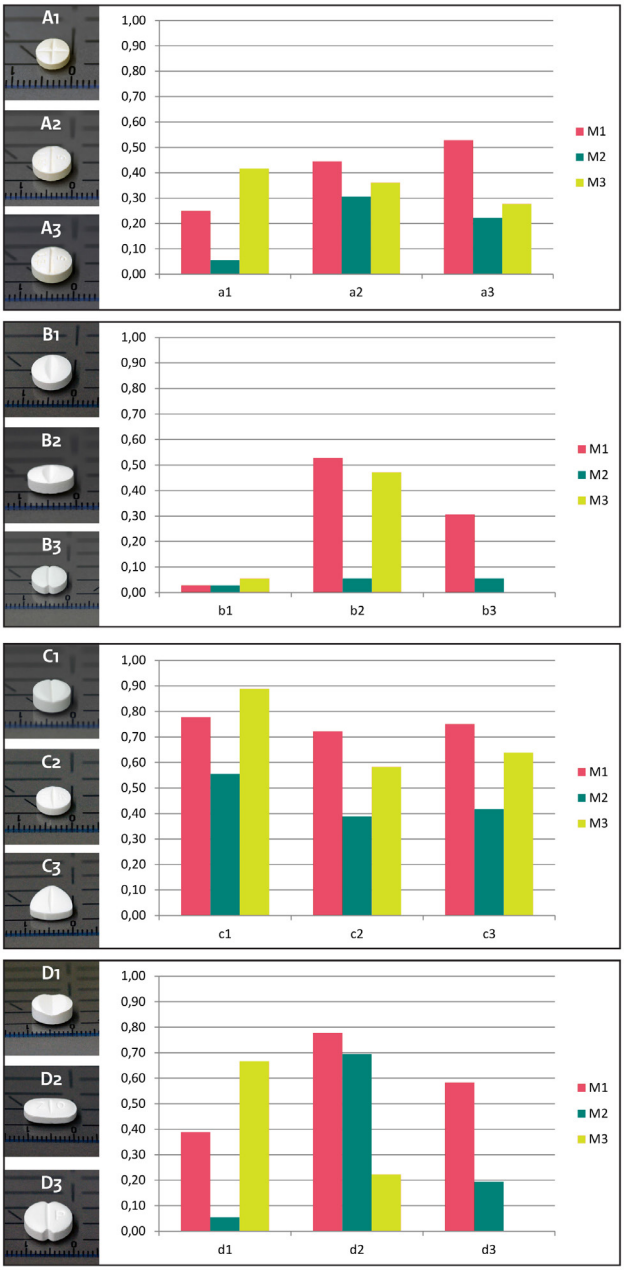
The relationship between age and the ability and accuracy of tablet breaking was further analysed by mixed-effects logistic regression modelling. According to the AIC, the most complex model (Model 6) best explained the ability of breaking between participants (Table 2; OR = 50.56, 95% CI = 25.02-108.03, P<0.001). Model 6 also best explained the accuracy of breaking. However, age was not significantly related to the accuracy of breaking (Table 3: OR = 1.19, 95% CI = 0.81-1.75, P=0.364). The other determinants gender, tablet and method of breaking were significant for both the ability and accuracy of breaking scored tablets. The c-indexes of these models were 0.945 and 0.851, respectively, meaning that the models' ability to discriminate between tablets that break or do not break (accurately) is very good.

Table 3 Odds ratios (ORs) and model characteristics for the accuracy of breaking

	Age *Reference: Older participants*		**Gender** *Reference: Female participants*		**AIC**
Models	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**	
Model 1: Random effect for participant; fixed effect for age	1.45 (1.06;1.97)	0.015	-	-	1676.77
Model 2: Model 1 + fixed effect for gender	1.31 (0.97;1.76)	0.074	0.65 (0.48;0.87)	0.005	1671.54
Model 3: Model 1 + fixed effects for gender and method of breaking	1.35 (1;1.82)	0.044	0.65 (0.48;0.88)	0.005	1668.2
Model 4: Model 1 + fixed effects for gender and tablet	1.1 (0.76;1.57)	0.605	0.52 (0.35;0.75)	0.001	1368.25
Model 5: Model 1 + fixed effects for gender, method of breaking and tablet	1.13 (0.79;1.61)	0.515	0.52 (0.35;0.75)	0.001	1368.99
Model 6: Model 5 + interaction between method of breaking and tablet	1.19 (0.81;1.75)	0.364	0.51 (0.34;0.77)	0.001	1315.94

CI = confidence interval; OR = odds ratio; AIC = aikake information criterion.

Figure 3 **Proportion of tablets that is broken by the older participants by the three methods of breaking**



M1= Breaking in between the fingers, with the use of nails. M2= Breaking in between the fingers, without the use of nails. M3= Breaking by pushing the tablet downward with one finger one a solid surface.

Discussion

The present study investigated the relationship between age and the ability to break scored tablets by hand, as well as between age and the accuracy of the same. Our findings demonstrate that older adults more frequently experience difficulties breaking scored tablets than young adults. Moreover, older adults were considerably less able to break tablets compared to young adults (OR = 50.56, P<0.001). Contrary to the ability of breaking, it was found that age was not related to the accuracy of breaking (OR = 1.19, P=0.364).

The findings of this study further show that a persons' ability to break a tablet is not only attributable to advanced age. Gender, the tablet itself and the method of breaking also contribute to an individuals' ability to break a tablet. To our knowledge, the effect of gender on the ability of breaking by hand was not identified before. In contrary, studies that allowed breaking by using a knife showed that gender was not predictive for the accuracy of breaking.[12, 25] Our finding that the ability and accuracy of breaking are influenced by the type of tablet, i.e. the physical characteristics of the tablet, confirms the findings of several other studies. The older participants most easily broke tablets C1-3 and D2. Tablets C2 and C3 are the thinnest tablets among our sample, with the exception of tablet A1. Previous studies showed that that thinner tablets are easier broken than thicker ones.[10, 18] Although tablet A1 was the thinnest tablet, it was also the tablet with the smallest diameter (5.7 mm) and therefore more difficult to handle, especially for the older participants. Tablet D2 is oblong shaped and has the largest diameter (11.6 mm) of our sample. Previous studies showed that oblong tablets are more easily broken than round ones, and that oblong tablets should have a diameter not smaller than 10 mm to be sufficiently breakable.[18, 19] A few studies showed the impact of the manual technique of breaking, although for only one or two tablets.[13, 20] The relation between the characteristics of a tablet and the method of breaking was however not addressed before.

The decreased ability of older adults to break tablets could be explained by a reduction in handgrip strength with advanced aging. This is supported by the finding that male participants broke more tablets compared to women, as men are known to have stronger grip strength than women.[26, 27] The absence of a relationship between age and the accuracy of breaking suggests that the accuracy of breaking is less affected by grip strength. Moreover, McDevitt et al. found that grip strength of men was inversely associated with the accuracy of tablet breaking.[12]

Implications for clinical practice

Problems with tablet breaking are not just a convenience issue. The occurrence of these problems will add to the regimen complexity, increasing the risk for non-adherence, medication errors and adverse drug reactions. The high prevalence of difficulties with breaking scored tablets observed in this study, stresses the need to diminish the occurrence of this problem. Manufacturers should avoid the use of score lines that are intended for dose adjustment, e.g. by producing tablets with dose strengths that correspond to the lower geriatric dose recommendations. In those situations where the presence of a score line is justified, manufacturers should validate the claimed functionality of the score line by breakability testing conducted in a population representative for the people that will break the tablet in daily practice. To date, the pharmacopoeial standards for the assessment of the performance of score lines do not define characteristics of the person performing the test.[23, 28] Furthermore, tablets may also contain a score line to facilitate swallowing instead of breaking in equal halves for dosing purposes. There are no regulatory requirements for these score-lines. The observed decreased ability of the older adults to break tablets that are scored for dosing purposes raises also a concern about the functionality of score lines intended to facilitate swallowing. It should be considered to assess the functionality of these score lines too.

From a patient perspective, health care providers could take an active role in improving therapeutic outcomes and reducing adverse consequences due to inaccurate dosing by addressing potential difficulties with breaking. Pharmacists should evaluate a person's ability to break a tablet accurately and determine the most suitable method of breaking. This should be done for each drug and each patient. In situations where a patient is not able to break the prescribed tablet, other solutions should be looked for. A different brand of the same product or a different dosage form could be more appropriate. When no alternatives are available, therapeutic substitution with an alternative that is available in an appropriate strength may sometimes be an option. Also, the tablets could be dispensed in equal halves by the pharmacy or another dosage form such as capsules could be compounded. Stability of the broken tablets should than however be guaranteed. This point could be addressed by drug product manufacturers.

As the ability of breaking is influenced by tablet characteristics, it is relevant that a persons' ability to break the prescribed tablet is re-evaluated when generic substitution or other brand dosage changes take place. Attention should be paid on any change in score line type, and therewith on instructions on the appropriate method of tablet breaking. Currently, information on the score line type, i.e. pressure sensitive or not, and instructions on how to break the tablet are not always present in the product information. For the twelve tablets investigated during this study, the patient information leaflet of only one tablet (A1) included

an instruction on how to break the tablet. It is recommended that the instructions on the appropriate method of tablet breaking become a mandatory part of the patient information leaflet for tablets with a score line.

Limitations

Our study has some limitations. It could be argued that the selection of participants from homes for elderly is not representative of community dwelling older adults. However, the people selected were living in either sheltered or so-called service accommodation, and were not eligible for help with the use of their medication. They all managed their own medication. The inclusion and exclusion criteria for the older adults were chosen to compile a "worst case" group of people that is required to break tablets for dosing purposes in daily practice. Likewise, the young adults represent a "best case" group. These two age groups represent both ends of the Gaussian distribution. Even among the young adults the results of breaking were not fully satisfactory.

The participants did not have to subdivide the tablets included in our study on a daily basis. Patients might overcome their difficulties when they get more familiar and experienced with the breaking of a certain tablet. On the other hand, in many countries generic substitution may take place more than once during a year, reducing the effect of training by breaking.
We might have unobserved confounding. The two groups of volunteers might differ not only with respect to the observed characteristics like age and sex, but also with respect to unobserved characteristics like frailty, finger size, grip strength etc., that might influence the outcome.

We did not investigate the breaking of unscored tablets and neither did we include the use of aids such as kitchen knives or tablet splitters, although both are used in practice. Breaking unscored tablets is considered unlicensed use, and the result is expected to be worse compared to breaking of scored tablets. Additionally, the basic principle should be that patients do not need aids such as splitting devices or knives to obtain the prescribed dose from scored tablets. Several studies suggest that these aids do not accurately halve tablets.[14, 29-33] In addition, patients may harm themselves using knives. The risk of harm may even be increased in patients who have impaired manual function, which is often the reason why they are not able to break tablets manually.

To our best knowledge, this is the first study to demonstrate the relationship between age and the ability to break scored tablets by hand. Furthermore, we included three manual techniques of breaking and a relatively high number of tablets with different characteristics compared to many other studies.

Conclusions

This study demonstrates that the breaking of scored tablets by hand was less successful in a population of older adults compared to a group with young adults. Health care providers should be aware that tablet breaking is not appropriate for all patients and for all drugs. To ensure safe self-management of medicines, breaking tablets should be avoided in older patients and the use of alternatives should be considered. In case tablet breaking is unavoidable, health care providers should asses a patient's ability to break tablets and provide instructions on the appropriate method of breaking.

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References

1. Hill-Taylor B, Sketris I, Hayden J, Byrne S, O'Sullivan D, Christie R. Application of the stopp/start criteria: A systematic review of the prevalence of potentially inappropriate prescribing in older adults, and evidence of clinical, humanistic and economic impact. J Clin Pharm Ther. 2013;38(5):360-72
2. Fastbom J, Johnell K. National indicators for quality of drug therapy in older persons: The swedish experience from the first 10 years. Drugs Aging. 2015;32(3):189-99
3. Ni Chroinin D, Ni Chroinin C, Beveridge A. Factors influencing deprescribing habits among geriatricians. Age Ageing. 2015
4. Scott IA, Hilmer SN, Reeve E, Potter K, Le Couteur D, Rigby D*, et al.* Reducing inappropriate polypharmacy: The process of deprescribing. JAMA Intern Med. 2015
5. Projovic I, Vukadinovic D, Milovanovic O, Jurisevic M, Pavlovic R, Jacovic S*, et al.* Risk factors for potentially inappropriate prescribing to older patients in primary care. Eur J Clin Pharmacol. 2016;72(1):93-107
6. Notenboom K, Beers E, van Riet-Nales DA, Egberts TC, Leufkens HG, Jansen PA*, et al.* Practical problems with medication use that older people experience: A qualitative study. J Am Geriatr Soc. 2014;62(12):2339-44
7. Rodenhuis N, de Smet PA, Barends DM. Patient experiences with the performance of tablet score lines needed for dosing. Pharm World Sci. 2003;25(4):173-6
8. Denneboom W, Dautzenberg MG, Grol R, De Smet PA. User-related pharmaceutical care problems and factors affecting them: The importance of clinical relevance. J Clin Pharm Ther. 2005;30(3):215-23
9. Quinzler R, Szecsenyi J, Haefeli WE. Tablet splitting: Patients and physicians need better support. Eur J Clin Pharmacol. 2007;63(12):1203-4
10. Spang R. [breakability of tablets and film-coated dragees]. Pharm Acta Helv. 1982;57(4):99-111
11. Gupta P, Gupta K. Broken tablets: Does the sum of the parts equal the whole? Am J Hosp Pharm. 1988;45(7):1498
12. McDevitt JT, Gurst AH, Chen Y. Accuracy of tablet splitting. Pharmacotherapy. 1998;18(1):193-7
13. Wilson MG, Kaiser FE, Morley JE. Tablet-breaking ability of older persons with type 2 diabetes mellitus. Diabetes Educ. 2001;27(4):530-40
14. Verrue C, Mehuys E, Boussery K, Remon JP, Petrovic M. Tablet-splitting: A common yet not so innocent practice. J Adv Nurs. 2011;67(1):26-32
15. Helmy SA. Tablet splitting: Is it worthwhile? Analysis of drug content and weight uniformity for half tablets of 16 commonly used medications in the outpatient setting. J Manag Care Spec Pharm. 2015;21(1):76-88
16. Rodenhuis N, De Smet PA, Barends DM. The rationale of scored tablets as dosage form. Eur J Pharm Sci. 2004;21(2-3):305-8
17. Quinzler R, Gasse C, Schneider A, Kaufmann-Kolle P, Szecsenyi J, Haefeli WE. The frequency of inappropriate tablet splitting in primary care. Eur J Clin Pharmacol. 2006;62(12):1065-73
18. van Santen E, Barends DM, Frijlink HW. Breaking of scored tablets: A review. Eur J Pharm Biopharm. 2002;53(2):139-45
19. van der Steen KC, Frijlink HW, Schipper CM, Barends DM. Prediction of the ease of subdivision of scored tablets from their physical parameters. AAPS PharmSciTech. 2010;11(1):126-32
20. van Vooren L, De Spiegeleer B, Thonissen T, Joye P, Van Durme J, Slegers G. Statistical analysis of tablet breakability methods. J Pharm Pharm Sci. 2002;5(2):190-8
21. Pautas E, Despres J, Peyron I, Golmard JL, Grange J, Koenig N*, et al.* [divisibility of warfarin and fluindione tablets tested in elderly patients and their family circle]. Geriatr Psychol Neuropsychiatr Vieil. 2011;9(2):171-7
22. Barends DM, Groot DW, Frijlink HW, Rodenhuis N, van der Steen JC. Development of an in vivo test procedure for the ease of breaking of scored tablets. Pharmeur Sci Notes. 2005;2005(1):27-30

23. European pharmacopoeia, monograph 0478, tablets. 8th ed. Strasbourg: Council of Europe; 2013.
24. Barends DM, Groot DW, van der Steen JC, de Kaste D, Frijlink HW. Results of a market surveillance study in the netherlands on break-mark tablets. Pharmeur Sci Notes. 2006;2006(2):1-7
25. Zaid AN, Ghosh AA. Compliance of scored tablet halves produced by palestinian pharmaceutical companies with the new european pharmacopoeia requirements. Arch Pharm Res. 2011;34(7):1183-9
26. Budziareck MB, Pureza Duarte RR, Barbosa-Silva MC. Reference values and determinants for handgrip strength in healthy subjects. Clin Nutr. 2008;27(3):357-62
27. Incel NA, Sezgin M, As I, Cimen OB, Sahin G. The geriatric hand: Correlation of hand-muscle function and activity restriction in elderly. Int J Rehabil Res. 2009;32(3):213-8
28. The international pharmacopoeia, dosage forms: General monographs: Tablets. 5th ed: World Health Organisation; 2015.
29. Peek BT, Al-Achi A, Coombs SJ. Accuracy of tablet splitting by elderly patients. JAMA. 2002;288(4):451-2
30. Polli JE, Kim S, Martin BR. Weight uniformity of split tablets required by a veterans affairs policy. J Manag Care Pharm. 2003;9(5):401-7
31. Hill SW, Varker AS, Karlage K, Myrdal PB. Analysis of drug content and weight uniformity for half-tablets of 6 commonly split medications. J Manag Care Pharm. 2009;15(3):253-61
32. Shah RB, Collier JS, Sayeed VA, Bryant A, Habib MJ, Khan MA. Tablet splitting of a narrow therapeutic index drug: A case with levothyroxine sodium. AAPS PharmSciTech. 2010;11(3):1359-67
33. van Riet-Nales DA, Doeve ME, Nicia AE, Teerenstra S, Notenboom K, Hekster YA*, et al.* The accuracy, precision and sustainability of different techniques for tablet subdivision: Breaking by hand and the use of tablet splitters or a kitchen knife. Int J Pharm. 2014;466(1-2):44-51

Chapter 3.2

Learning from patients: identifying design features of medicines that cause medication use problems

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Abstract

Usability is a key factor in ensuring safe and efficacious use of medicines. However, several studies showed that people experience a variety of problems using their medicines. The purpose of this study was to identify design features of oral medicines that cause use problems among older patients in daily practice. A qualitative study with semi-structured interviews on the experiences of older people with the use of their medicines was performed (n=59). Information on practical problems, strategies to overcome these problems and the medicines' design features that caused these problems were collected. The practical problems and management strategies were categorised into 'use difficulties' and 'use errors'. A total of 158 use problems were identified, of which 45 were categorised as use difficulties and 113 as use error. Design features that contributed the most to the occurrence of use difficulties were the dimensions and surface texture of the dosage form (29.6% and 18.5%, respectively). Design features that contributed the most to the occurrence of use errors were the push-through force of blisters (22.1%) and tamper evident packaging (12.1%). These findings will help developers of medicinal products to proactively address potential usability issues with their medicines.

Introduction

Medicinal products should be reliable and practicable to use by patients, regardless of age and physical ability. However, several studies showed that patients experience problems with the use of medicines, such as difficulties in opening packaging and accessing the contents, difficulties with the identification of medicines, difficulties breaking tablets for dosing purposes and difficulties swallowing medicines.[1-10] The proportion of patients that experience problems using their medicines increases with advanced age due to decreased mental, sensory and physical abilities. A previous study showed that older people experience a broad range of practical problems with the use of their medicines and that incorrect medication use caused by these problems may have clinical consequences.[5] The problems experienced by especially older users indicate that usability is insufficiently taken into consideration during the development of medicinal products. However, usability is a key factor in ensuring safe and efficacious use by patients.

Contrary to the situation for medicinal products, the evaluation of usability plays a crucial role in the development and design of medical devices. Errors caused by inadequate medical device usability and design shortcomings are a recognised cause for concern and have to be reduced as far as possible. This is usually covered as part of the risk management process that is applied during the entire life cycle of a medical device. During the design and manufacture of medical devices it is mandatory to reduce the risk of use error due to ergonomic features of the device, while considering the knowledge, experience, and training and where applicable the medical and physical conditions of intended users.[11] Processes like Human Factors Engineering (HFE) and risk management techniques such as Failure Mode and Effect Analysis (FMEA) are commonly employed to identify potential use errors, which can then be eliminated or reduced as far as possible by a policy of inherently safe design.[12, 13] HFE examines how users interact with the device in order to improve human performance by designing devices that take account of the cognitive and physical capabilities and limitations of users. FMEA evaluates the risk of use errors and their potential effects. The results of the risk analysis highlight the shortcomings in the design. A detailed task-analysis of everything a user can do when interacting with a device can be helpful in these processes.

Similar approaches can be adopted during the development and design of medicinal products. Identification and awareness of the specific elements in medicinal product design that potentially hinder the proper use of medicines may contribute to reduce such problems. Experiences from daily practice with comparable products will help medicine developers to anticipate on potential usability issues during the development process of new products. The aim of the present qualitative study was to identify design features of medicinal products that cause use problems among older patients in daily practice.

Material and methods

Study design and recruitment

A qualitative study with semi-structured interviews on practical problems that elderly people experience with the use of their medicines was performed.[5] The participants were recruited from a community pharmacy belonging to the Utrecht Pharmacy Practice Network for Education and Research[14] as well as from the geriatric outpatient ward of the University Medical Centre Utrecht (UMCU), both in the Netherlands. Participants were eligible if they were community-dwelling, aged 70 years or older and used at least three different oral prescription medicines daily. Individuals were excluded if their medication was entirely managed by professional help or by the participant's carer, or if the medication was delivered in multi-compartment pill boxes or in other multi-dose dispensing systems. Eligible people were approached by their community pharmacist or geriatrician. Recruitment of participants continued until data saturation was achieved. This was achieved when no new problems and solutions emerged in five consecutive interviews.

This study was not subject to the Medical Research Involving Human Subjects Act (WMO). The study was conducted in compliance with the requirements of the UPPER institutional review board (http://www.uu.nl/vkc/upper). For this type of study, informed consent is not required in the Netherlands.

Data collection

The experiences of older patients with the use of their oral medicines were collected through semi-structured face-to-face interviews. The interviews were guided by a flexible topic list based on problems with medication use reported in the literature. This included any practical problems with the use of their medicines and their strategies to overcome these problems.[5] The topic list ensured that all key aspects of the medication use process were covered. Posing open, direct questions allowed to elicit detailed narratives and stories of the participants' experiences with the use of their medicines.

Before the start of the interview, participants were asked to collect all their medicines; these were verified with the dispensing record provided by their community pharmacy. During the interview, the marketing authorisation number and specific design features of the medicines that were related to the use problems were collected. This comprised the design features of the dosage form, the packaging and any dosing device, e.g. the type of dosage form, the colour, shape, size, palatability, presence of coating and break mark on a medicine, type and characteristics of the outer and immediate packaging, and, if applicable, the type of dosing device and its characteristics.

Data processing and analysis

The audio recordings of the interviews were transcribed verbatim and anonymised. The transcripts were imported in ATLAS.ti software for coding and analysis (version 7.0, Scientific Software Development GmbH, Berlin, Germany). Reliability and validity of the transcribed data were ensured by the combination of voice recording, field notes and photographs. The transcripts were used to explore the problems with the use of medicines. The practical problems, coping strategies and design features of the medicines were coded in the transcripts.[5]

Next, the practical problems and their coping strategies were categorised into 'use difficulties' and 'use errors' by two researchers independently (KN and MB):

- A 'use difficulty' includes the situation were a participant experiences difficulty performing a task but is able to complete the task without help or coping strategy.
  An example of a use difficulty is a patient having difficulty removing a cap from a container but after some time of trying, he or she finally succeeds.

- A 'use error' includes the situation were a participant is unable to perform a task as intended and either needs help or applies a strategy to complete the task.
  Examples of use errors are a patient who is not able to remove a cap from a medicine container by his- or herself and therefore asks another individual to remove the cap, or a patient who needs to use a knife to open the tamper evident feature on the cap of the container.

This approach was derived from international standards for medical devices.[12, 13] The two researchers discussed any disagreements until consensus was reached. The consistent categorisation into use difficulties and use errors was achieved by 'constant comparison'.

To prioritise the few most important design features with the greatest cumulative contribution to the occurrence of medication use problems, the design features related to the use difficulties and use errors were plotted in decreasing order of relative frequency.

Results

Fifty-nine people participated in this study. Their median age was 78.0 years (SD 6.2; range 70-92), and 38 were women (64.4%). On average, participants used 6.9 oral prescription medicines daily (SD 2.2; range 3-12) at the time of the interview. Six of the 59 patients

(10.2%) experienced no problems with the use of their medicines. A total of 158 use problems were identified, of which 45 were categorised as use difficulties and 113 as use errors. The identified use difficulties and use errors along with the related design shortcomings for the tasks and subtasks of the medication use process are listed in Table 1. Most use difficulties concerned swallowing of medicines (37.8%), followed by the removal of medicines from a blister (13.3%). Most use errors concerned the removal of medicines from a blister (31.9%), followed by the opening of containers (15.9%).

The design features that attributed to the use problems were plotted as presented in Figures 1(a) and 1(b) for use difficulties and use errors, respectively. The charts illustrate that the design features that contributed the most to the occurrence of use difficulties were the dimensions of the dosage form (29.6%) and the surface texture of the dosage form (18.5%). With regard to the occurrence of use errors, the design features that contributed the most were the push-through force of blisters (22.1%) and tamper evident features (12.1%).

The use problems are described in more detail below, along with representative interview quotes. As the interviews were conducted in Dutch, the quotes are translated from Dutch to English.

Use problems related to the push-through force of blisters
There were 35 reports of problems with the extraction of medicines from blister packaging caused by a too high push-through force:

Then, on the back, I move the potato knife along one side. And when I press a little, I can get it out.
(Woman, 83 years, example of a use error)

This costs a little bit of effort though. There are three that I find a little bit difficult. To me. Have a look. I can still do it. Don't give up. And when it doesn't work out with this one, I try another one and get back to this one thereafter.
(Woman, 86 years, example of a use difficulty)

In 15 cases the extraction resulted in damage to the dosage form, i.e. breaking or crumbling of tablets (n=12) and denting or opening of capsules (n=3). Nine of these twelve tablets concerned a tablet with a score line:

This one often breaks. When I push it out. Look, because it has a line. A score line. And that one snaps almost every time. I always have to look, to see where the other halve went. That

is unwieldy. Very often it lies somewhere else.
(Man, 71 years, example of a use error)

Use problems related to tamper evident closures
Tamper evident closures caused problems with the opening of containers (n=13) and cartons (n=6). The containers were equipped with plastic, so-called breakable or tear-away closures that have a portion that breaks on opening:

Look, it has a band. And you have to pull it open, which costs a huge effort. I also have to turn this and I am not able to do this. So, my cleaning lady comes every Wednesday, and then I ask her in case a bottle needs to be opened. I think these are worthless bottles.
(Woman, 86 years, example of a use error)

The cartons were closed with glue. Perforations were applied to facilitate opening, however, these openings were not visible to the participants:
I use a scissor, there is no other way to open it. (interviewer points out the perforation line on the carton). *I can't see that. I can barely see it while I wear my glasses! It is a good thing I know now.*
(Woman, 83 years, example of a use error)

Use difficulties and errors associated with break marks on tablets were associated with difficulty of breaking, breaking into unequal portions or crumbles, and with unintended breaking when the tablet is extracted from the blister.

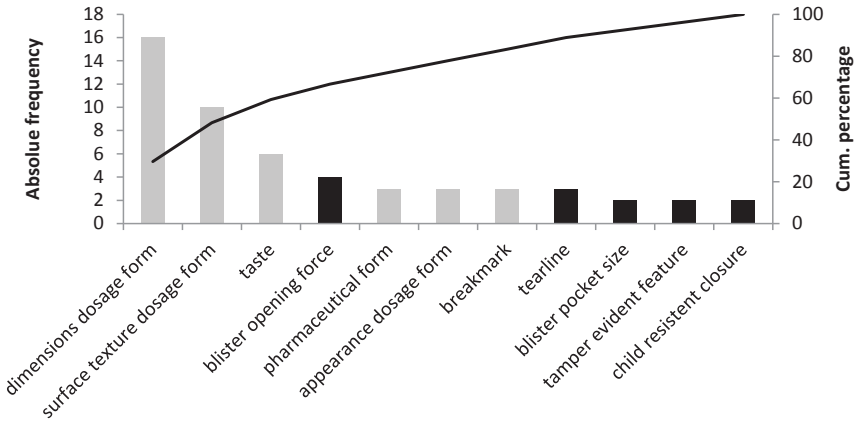
Use problems related to the dimensions of a dosage form
Use difficulties and errors associated with the dimensions of a dosage form included problems holding a medicine and problems swallowing in which the medicine became stuck in the throat. Use difficulties and errors associated with the surface texture of a dosage form concerned problems swallowing in which the medicine became stuck in the throat. Participants explained the lodging of the dosage forms by a large size and quick disintegration of the product:

These are large. I have difficulties with it. It is a problem. I am afraid, just before I take it, that I can't swallow it. It is a little bit of fear too, I guess. I just give it a try. I gargle a little and so, awful. Suddenly, I swallow. It is something of which I always think: yech, I have to. The other ones go down easily, but this one not.
(Woman, 72 years, example of a use difficulty)

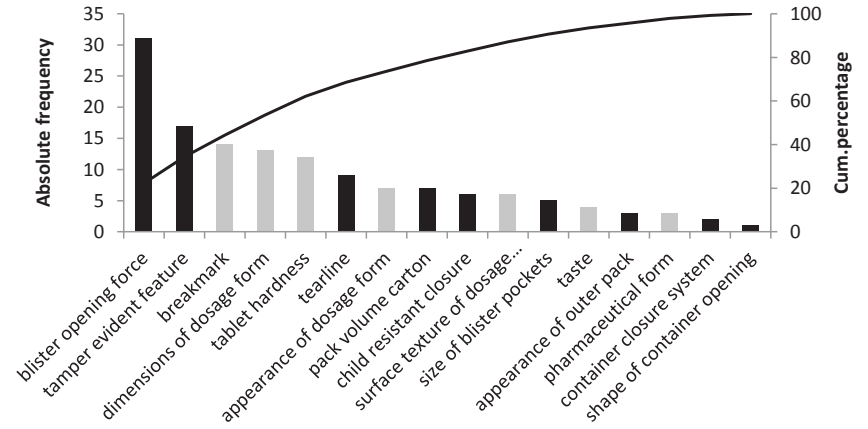
Look, these, I always take them with water, but sometimes they get stuck, you know. They are a little brittle and get stuck half way. Then I have to take a large sip of water again. Thus, I can't swallow it easily. I have no difficulties with the other ones, but these things appear to be less solid, they quickly start melting, you know, and it gets stuck and I need to drink a good amount of water otherwise it remains stuck. Then, it goes well.
(Man, 72 years, example of a use difficulty)

Further analysis of these design features showed that most of the problems in which the medicine became stuck in the mouth or throat (n=16) occurred with uncoated tablets (n=11), of which nine tablets had a diameter ranging between 0.5-1.0 cm. The same problem concerned three coated tablets, of which two tablets had a diameter of more than 1.5 cm and one tablet a diameter between 0.5-1.0 cm. The problem was also reported for two capsules, both with a size larger than 1.5 cm.

Figure 1 **Pareto charts representing the design features that attributed to use difficulties (a) and use errors (b)**



(**a**) Design features that attributed to use difficulties in decreasing order of relative frequency.



(**b**) Design features that attributed to use errors in decreasing order of relative frequency. The light grey bars represent design features that are related to the dosage form, the black bars represent design features related to packaging.

Table 1	Use difficulties (UD) and use errors (UE), and related design shortcomings of the packaging (A) and dosage form (B)		
A. Design shortcomings of packaging	**UD (n)**	**UE (n)**	**Problems experienced with packaging**
➢ **Appearance of packaging**			
The appearance of the outer pack is insufficiently distinct from other products		3	The patient mixed-up look-a-like packaging
➢ **Tamper evident closures**			
Perforated opening of tamper evident closure on the carton is poorly visible		3	The patient used sharp kitchenware to open the glued flaps
		3	The patient damaged the carton to open the glued flaps
The tamper evident closure of the container is too difficult to open	2		The patient has difficulty opening the tamper-evident closure but succeeds
		6	The patient cannot open the tamper-evident closure
		5	The patient used (sharp) kitchenware to open the tamper-evident closure
➢ **Child-resistant closures**			
The child resistant closure of the container is too difficult to open	2		The patient has difficulty with the opening of the child resistant closure but succeeds
		1	The patient cannot open the child resistant closure
		2	The patient has difficulty with the opening of the child resistant closure (with desiccant inside) and therefore leaves cap not properly closed
		3	The patient has difficulty with the opening of the child resistant closure (with desiccant inside) and therefore transfers the contents to another container
➢ **Regular closure system**			
The closure system is too difficult to open		1	The patient used sharp kitchenware to open the container and then leaves cap not properly closed
The cap of the container breaks tablets when fully packed.		1	The patient removes the harmonica plug on the inside of the cap because it crushes/breaks the tablets
➢ **Container**			
The opening of the container is too small		1	The patient has difficulty removing tablets from the container and transferred them to another container
➢ **Tearlines**			
Tearline of wrapper is too difficult to use	1		The patient has difficulty opening the wrapper but succeeds
		2	The patient used sharp kitchenware to open wrapper
Tearline on blister is too difficult to use		2	Patient uses sharp kitchenware to separate units because the tearline cannot be teared
No tearline on blister		1	Patient uses sharp kitchenware to separate units because there is no tearline
A label is placed on the tearline between sachets		1	Sachet opens following separation

A. Design shortcomings of packaging	UD (n)	UE (n)	Problems experienced with packaging
Tearline between sachets is too difficult to use	2		The patient has difficulty separating sachets but succeeds
		2	The patient uses sharp kitchenware to separate sachets to avoid leaking
Tearline between plastic ampoules too difficult to use		1	More than one ampoule opens
➢ **Push-through force of blister**			
The push-through force of the blister is too high	4		The patient has difficulty pushing the tablet out but succeeds
		3	The capsule opens/dents while pushing it out.
		4	The patient has difficulty pushing the tablet out but succeeds although also the tearline tears
		6	The patient has difficulty pushing the tablet out but succeeds by using sharp kitchenware to pierce the lidding foil
		5	The patient has difficulty pushing the tablet out but succeeds by using his nails to pierce the lidding foil. Nails regularly get chopped of by doing this.
		1	The patient has difficulty pushing the tablet out and therefore transfers all tablets to a container
➢ **Push-through force of blister & tablet hardness**			
The push-through force of the blister is too high and/or tablet hardness is insufficient		2	The unscored tablet breaks/crumbles while pushing it out, the patients administers the resulting pieces
		1	The dispersible tablet breaks/crumbles while pushing it out
➢ **Push-through force of blister & tablet hardness & presence of score line**			
The push-through force of the blister is too high, presence of break mark and/or tablet hardness is insufficient		9	The scored tablet breaks/crumbles while pushing it out, the patients administers the resulting pieces or takes another dosage
➢ **Size of blister pockets**			
Size of the blister pockets is too small and/or distance between pockets is too small		2	The patient has difficulty placing his finger on one pocket but succeeds by pushing it with two nails. Nails regularly get chopped of by doing this.
		1	The patient has difficulty placing his finger on one pocket and removes two tablets at once
		1	The patient uses sharp kitchenware to separate pockets
Size ratio between blister pocket and tablet is too large	1		The patient experiences difficulty locating the tablet in the pockets but succeeds
	1		The pocket collapses when it is pushed but tablet comes out.
		1	The pocket collapses when it is pushed but no tablet comes out. Patient uses sharp kitchenware to cut the lidding foil
➢ **Pack volume**			
Pack too full		7	The patient discarded the package insert

B. Design shortcomings of the dosage form	UD (n)	UE (n)	Problems experienced with packaging
➢ **Appearance of the dosage form**			
The appearance of the dosage form is insufficiently distinct from other products		7	The patient has difficulty differentiating tablets
	1		The patient has difficulty differentiating tablets but succeeds by differences in embossment
	2		The patient has difficulty differentiating tablets but succeeds by keeping them in the blister and placing marks on the blister.
Dose marking is insufficiently visible	1		The patient has difficulty reading the dose marking on the measuring cup but succeeds
➢ **Dimensions of the dosage form**			
The dimensions of the dosage form are too small	4		The patient has difficulty holding the tablet but succeeds.
		7	The patient has difficulty holding the tablet. They often drop on the floor. The patient picks it up and takes it or takes another one.
	1		The patient has difficulty holding the tablet but succeeds by wetting a finger and attach tablet to it.
	1		The patient has difficulty locating the product in mouth which makes swallowing difficult but succeeds
➢ **Dimensions & surface characteristics of the dosage form**			
The dimensions of the dosage form are too large and/or the surface of the dosage form is inconvenient	10		The patient has difficulty swallowing because the medicine becomes stuck in the mouth/throat but succeeds; without solution, by taking this medicine before others or by taking additional water
		6	The patient has difficulty swallowing because the medicine becomes stuck in the mouth/throat but succeeds by taking it with semi-solid food
➢ **Tablet hardness & push-through force of blister**			
The push-through force of the blister is too high and/or tablet hardness is insufficient		2	The unscored tablet breaks/crumbles while pushing it out, the patients administers the resulting pieces
		1	The dispersible tablet breaks/crumbles while pushing it out
➢ **Tablet hardness & presence of score line & & push-through force of blister**			
The push-through force of the blister is too high, presence of break mark and/or tablet hardness is insufficient		9	The scored tablet breaks/crumbles while pushing it out, the patients administers the resulting pieces or takes another dosage

B. Design shortcomings of the dosage form	UD (n)	UE (n)	Problems experienced with packaging
➢ **Break marks**			
Break mark does not function well	1		The patient has difficulty breaking scored tablets for ease of swallowing but succeeds
	2		The patient has difficulty breaking scored tablets for dosing purposes but succeeds
		1	The patient is not able to break the tablet for dosing purposes but succeeds by using tablet splitter
		2	The tablet does not break in equal halves or crumbles when breaking for dosing purposes. Patient takes another tablet
		1	The tablet does not break in equal halves when breaking for dosing purposes. Patient takes unequal parts anyway
		1	The tablet does not break in equal halves when breaking for dosing purposes. Patient uses tablet splitter
➢ **Taste of the dosage form**			
The dosage form has an unpleasant taste	6		The patient has difficulty swallowing because the medicine has an unpleasant flavour but succeeds; without solution, by taking this medicine before others or by taking additional water
		3	The patient has difficulty swallowing because the medicine has an unpleasant flavour but succeeds by taking it with semi-solid food
		1	The patient has difficulty taking the suspended dispersible tablet because it has an unpleasant flavour. The tablet is swallowed whole.
➢ **Complexity of the dosage form**			
User does not understand how to use the pharmaceutical form		1	The patients swallows the dispersible tablet as a whole because it does not dissolve completely
	3		The dispersible tablet does not dissolve completely. The patient either leaves the residue or adds extra water to administer residue
		1	The patient uses a spoon to crush particles because dispersible tablet does not dissolve completely
		1	The patient uses boiled water to dissolve dispersible tablets because otherwise it does not dissolve completely

Discussion

This study identified the specific design features of medicinal products that are associated with medication use problems among older people. Physical constraints, such as impaired vision, reduced manual dexterity or strength, and loss of touch and sensitivity in the hands can interfere with the user's ability to interact with the product and cause use problems. The design features that contributed the most to the occurrence of use errors were the push-through force of blisters and the opening of tamper evident closures. The results provide evidence that optimising the design of medicinal products will mitigate the risk of medication use problems.

Strengths and limitations

Although previous studies reported many problems with the use of medicines, an investigation of the design features of medicines that contribute to the occurrence of use problems had yet to be made. The collection of information reported by participants introduced the risk of reporting bias and recall bias. Therefore, all medicines used by the participants were present during the interview. This helped the participants to bring up any problems as well as to demonstrate the experienced problems. In addition, it allowed the interviewer to notice any unreported problems, e.g. torn cartons or the presence of a potato knife among the medicines. This direct way of observation has high validity in unravelling what really happens during the daily use of the medicines.

Only problems with the use of oral medicines were investigated. Other administration routes, e.g. by inhalation or injection, are often more complex and introduce more opportunities for patients to encounter use problems. Furthermore, patients are not the only users of medicines. Several products are administered to patients by health care providers, such as parenteral injections or infusions.

Implications for practice

The occurrence of medication use problems has not gone unnoticed. Regulators recently stressed the impact of product design on medication use. Both the European Medicines Agency's (EMA) and the Food and Drug Administration (FDA) published guidance documents on minimising the risk of medication errors related to product design. These guidances advocate that medicine developers proactively consider all aspects of the design of the product, and conduct a suitable analysis to identify and assess potential for medication errors.[15, 16] Medication errors are commensurable to use errors with medical devices. Like use errors with medical devices, medication errors can be attributable to product design. For both medical devices and medicinal products, use errors can cause a hazardous situation,

however, they do not always cause a hazardous situation or lead to harm. A use error may cause harm in one situation but not in another, e.g. a tablet that breaks in pieces following extraction from the blister will not cause a problem when it concerns an antacid, while the same issue with tablet breaking will cause a problem when it concerns a product with a small therapeutic window. Use difficulties, i.e. the situation where a patient is able to perform a task but only with difficulty, are quite often overlooked. However, convenience issues are critical for therapeutic outcomes if it causes non-adherence. Moreover, use difficulties can turn into use errors at a certain moment. Many of the use errors identified in the current study concerned use difficulties for which the participants applied a strategy to overcome the difficulty. These strategies may result in a hazardous situation or cause harm to the patient because the product is not used as intended. Hazardous situations do not always have to be related to the use of the medicinal product itself. The use of sharp kitchenware such as knives can also cause harm to the patient.

The FDA and EMA guidance provide examples of medication errors and of design features which may reduce the risk of medication errors. Little attention is given to the usability of packaging though. This study shows that blister lidding foils and tamper verification features on packaging largely contribute to the occurrence of use errors among older people. The errors associated with tamper evident packaging, such as folding boxes closed with glue and containers equipped with plastic tear-away closures, are particularly challenging. With publishing of the Commission Delegated Regulation (EU) 2016/161, that supplements Directive 2001/83/EC, with detailed rules for the safety features appearing on the packaging of medicinal products for human use, pharmaceutical companies are required to fulfil the requirements of the Falsified Medicines Directive by 9 February 2019.[17] This implies that by then all pharmaceutical packaging available in Europe needs to be equipped with an anti-tampering device, i.e. a device that reveals irreversibly whether the container has been opened.[17, 18] Consequently, the prevalence of problems with the accessibility of pharmaceutical packaging will increase. In the current study, participants reported they could not see the perforation line to facilitate the opening of the cartons closed with glue or they were not able to break the plastic tear-away closure. Making perforation lines more clearly visible and tear-away closures easier to break will improve the usability of tamper-proof packaging among those suffering from impaired visual acuity or reduced manual strength.

Problems with pushing medicines out through the blister lidding foil could be overcome by peel-off blisters, however usability problems have been reported for these foils too.[6, 19] Problems with the opening of blister packages were not only caused by a high push-through force, but also with a small size of the pockets or small distance between the pockets and

with too much movability of the medicine in the pocket. A recent study confirmed the relevance of a good fit of the dosage form in the blister pocket, i.e. allowing palpability and limited movability of the dosage form.[20] The use errors identified in the current study that were associated with child resistant closures indicate that the use of child resistant closures with integrated desiccant needs to be reconsidered, especially when used among an older population. A difficult-to-open-cap that at the same time has the critical function to protect the medicines inside the container from degradation by moisture appears to be an inappropriate design choice. Patients may not close the container or transfer the contents to other packaging.

Conclusion

Use difficulties and errors encountered by people with the daily use of their medicines result from the interaction between the user and the medicinal product. Medicinal products should be designed to meet the needs, capabilities, and limitations of the patients for who they are intended, taking into account for example age and physical ability. Patient-centred design of medicinal products will enable patients to use their medicines safely and easily. As for medical devices, areas for design improvement can be identified through human factor and/or usability engineering. This study identified design features of oral medicinal products that contribute to the occurrence of use problems among an older population. These findings will help developers of medicinal products to proactively address potential usability issues with their medicines.

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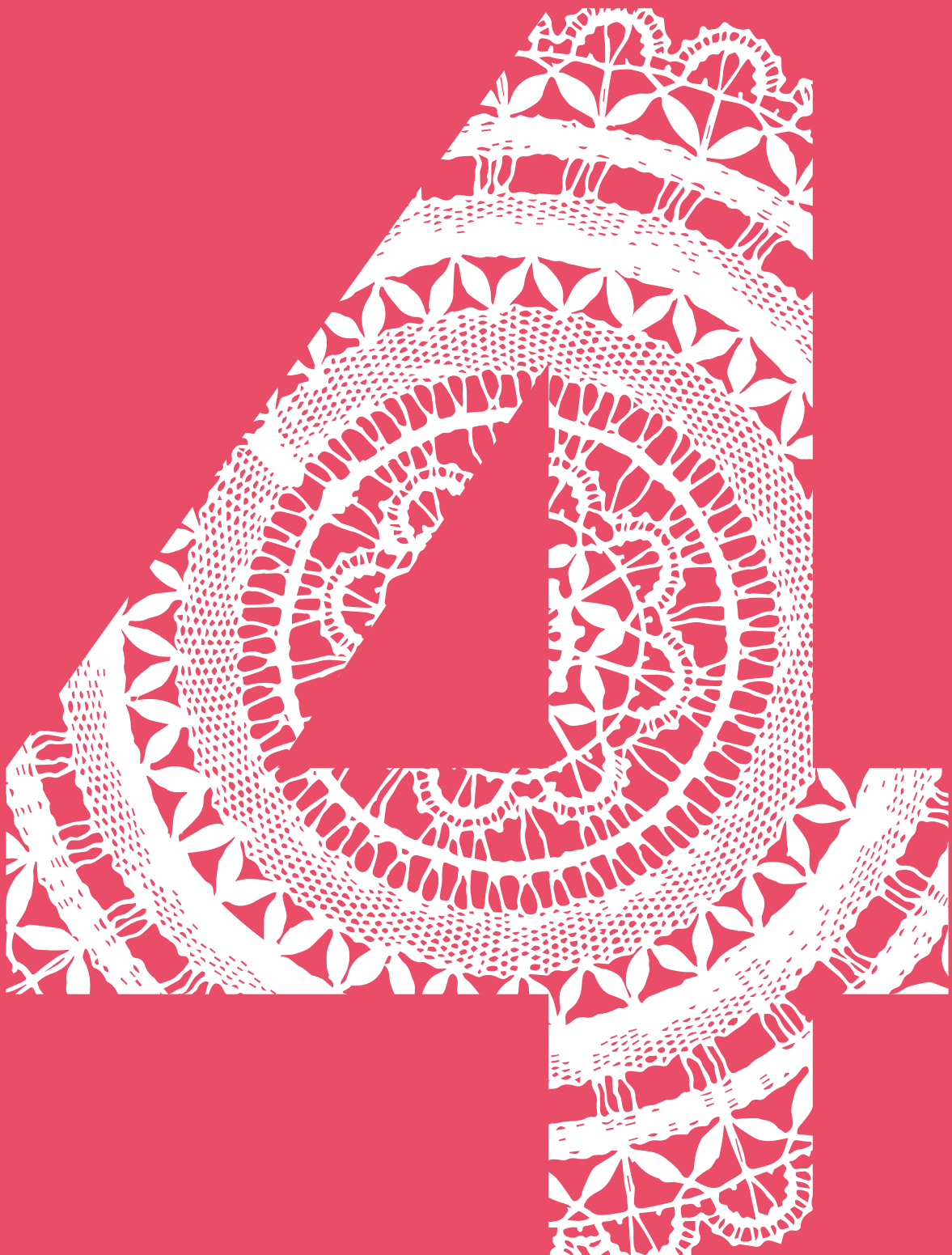
References

1. Atkin PA, Finnegan TP, Ogle SJ, Shenfield GM. Functional ability of patients to manage medication packaging: A survey of geriatric inpatients. Age Ageing. 1994;23(2):113-6
2. Beckman A, Bernsten C, Parker MG, Thorslund M, Fastbom J. The difficulty of opening medicine containers in old age: A population-based study. Pharm World Sci. 2005;27(5):393-8
3. Kelly J, D'Cruz G, Wright D. Patients with dysphagia: Experiences of taking medication. J Adv Nurs. 2010;66(1):82-91
4. Marquis J, Schneider MP, Payot V, Cordonier AC, Bugnon O, Hersberger KE*, et al.* Swallowing difficulties with oral drugs among polypharmacy patients attending community pharmacies. Int J Clin Pharm. 2013;35(6):1130-6
5. Notenboom K, Beers E, van Riet-Nales DA, Egberts TC, Leufkens HG, Jansen PA*, et al.* Practical problems with medication use that older people experience: A qualitative study. J Am Geriatr Soc. 2014;62(12):2339-44
6. Philbert D, Notenboom K, Bouvy ML, van Geffen EC. Problems experienced by older people when opening medicine packaging. Int J Pharm Pract. 2014;22(3):200-4
7. Schiele JT, Quinzler R, Klimm HD, Pruszydlo MG, Haefeli WE. Difficulties swallowing solid oral dosage forms in a general practice population: Prevalence, causes, and relationship to dosage forms. Eur J Clin Pharmacol. 2013;69(4):937-48
8. Sormunen E, Nevala N, Sipilä S. Critical factors in opening pharmaceutical packages: A usability study among healthcare workers, women with rheumatoid arthritis and elderly women. Packag Technol Sci. 2014;27(7):559-76
9. Thwaites JH. Practical aspects of drug treatment in elderly patients with mobility problems. Drugs Aging. 1999;14(2):105-14
10. Liu F, Ghaffur A, Bains J, Hamdy S. Acceptability of oral solid medicines in older adults with and without dysphagia: A nested pilot validation questionnaire based observational study. Int J Pharm. 2016
11. Council directive 93/42/eec of 14 june 1993 concerning medical devices, as amended by directive 2007/47/ec of the european parliament and of the council of 5 september 2007., European Commission.
12. Medical devices - part 1: Application of usability engineering to medical devices, IEC 62366-1:2015,IDT, European Committee for Electrotechnical Standardization (2015).
13. Medical devices - application of risk management to medical devices, EN-ISO 14971:2007 (corrected and reprinted 2012-07), CEN/CENELEC (2012).
14. Koster ES, Blom L, Philbert D, Rump W, Bouvy ML. The utrecht pharmacy practice network for education and research: A network of community and hospital pharmacies in the netherlands. Int J Clin Pharm. 2014;36(4):669-74
15. Good practice guide on risk minimisation and prevention of medication errors, EMA/606103/2014. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) (2015).
16. Safety considerations for product design to minimize medication errors, Food and Drug Administration. Center for Drug Evaluation and Research (CDER) (2016).
17. Commission delegated regulation (eu) 2016/161 of 2 october 2015 supplementing directive 2001/83/ec of the european parliament and of the council by laying down detailed rules for the safety features appearing on the packaging of medicinal products for human use, European Commission (2015).
18. Directive 2011/62/eu of the european parliament and the council of 8 june 2011 amending directive 2001/83/ec on the community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products, European Commission (2011).
19. Muhlfeld L, Langguth P, Hausler H, Hagels H. Influence of blister package design on usability among older adults. Int J Clin Pharm. 2012;34(4):553-60
20. Braun-Munker M, Ecker F. Ease of opening of blistered solid dosage forms in a senior citizens target group. Int J Pharm. 2015



Chapter 4

Approaches to prevent usability problems with medicines

4.1

Chapter 4.1

Pharmacy technicians attention to problems with opening medicine packaging

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Abstract

Background

Pharmacy technicians seem to be well equipped to engage in conversations with patients about their experiences and problems with medication, but it is unclear whether or not they systematically explain or demonstrate to patients how to use medication packaging.

Objective

To explore to what extent pharmacy technicians identify problems with opening medicine packaging and how they assist patients in solving these problems.

Methods

We conducted a cross-sectional study that comprised semi-structured interviews, with 31 pharmacy technicians in 31 pharmacies, to assess the occurrence and type of difficulties with packaging and to suggest solutions.

Results

All pharmacy technicians recognise the occurrence of packaging problems, though patients rarely report them at the pharmacy counter. Not all pharmacy technicians are familiar with opening all packaging forms, but they all describe ways to find out how to open them, which usually only happens after patients bring up problems. Solutions suggested by the pharmacy technicians include informing and counselling, changing or manipulating the packaging, and providing assisting tools.

Conclusions

This study shows that although pharmacy technicians are aware that medication packaging can cause problems and are able to name or find out solutions to all these problems, there is no systematic attention for packaging at drug dispensation in most pharmacies.

Discussing the handling of medication packaging should become a fixed part of drug dispensation counselling. Pharmacists should draw up working procedures to support pharmacy technicians in their counselling activities.

Introduction

Guidelines developed by the Royal Dutch Pharmaceutical Society state that correct medication use should be addressed during dispensation[1], but practical issues such as usability of the packaging do not receive much attention. Problems with opening medicine packaging such as blisters or bottles can cause difficulties in daily use, especially for older people or people with rheumatoid arthritis (RA).[2-7] One previous study showed that most of the practical problems with medication concerned this issue[8]; another study showed that 1 in 4 patients using omeprazole experienced problems with opening the packaging.[9] Some of these problems could have been prevented with proactive counselling on how to open the packaging or by supplying tools designed to help open certain packaging forms.

In the Netherlands, pharmacy technicians engage in patient contact at the counter more frequently than pharmacists.[10] Training and work roles of pharmacy technicians may vary between countries. In the United States, technicians are usually involved in areas including administration (prescription entry, inventory control, filling bottles with prescribed medication, and labelling them) and answering simple questions (referring patients to a pharmacist for medication information), to free up the pharmacist to focus on other functions such as patient counselling.[11, 12] In the United Kingdom and Belgium, for instance, pharmacy technicians are given other responsibilities, including advising patients on correct and safe medication use.[13, 14] Technicians in the Netherlands are professionally trained to counsel patients about their medication.[15, 16]

The aim of this study was to explore to what extent (and how) pharmacy technicians identify problems with opening medicine packaging and how they assist in solving these problems. Problems with administration of medication are outside the scope of this study.

Methods

Setting and participants

In this cross-sectional study, pharmacy students in their final (sixth) year conducted semi-structured interviews with pharmacy technicians in the pharmacies where they were doing their internship (duration 6 weeks). Students had not been employed in the pharmacy prior to their internship.

A convenience sample of 31 community pharmacies affiliated with the Utrecht Pharmacy Practice network for Education and Research (UPPER) was selected because these pharmacies

were supervising pharmacy student interns during the period of data collection. These pharmacies covered areas in the centre, northwest, and southwest of the Netherlands, in mostly urban settings. The pharmacist selected the technician who had the most experience as well as frequent patient contact, and this technician was interviewed for the study.

The study was conducted in compliance with the requirements of the UPPER Institutional Review Board of the Pharmacoepidemiology and Clinical Pharmacology Division of Utrecht University.

Interview

Interviews were guided with an interview questionnaire that contained mostly open-ended questions concerning the occurrence of reported problems with opening medicine packages, identification of patient groups at high risk of problems, types of problems, and counselling regarding the opening of medicine packaging by technicians. Specific attention was given to push-through and peel-off blisters, pill bottles, dropper containers, suppositories, and tubes (see the appendix for the questionnaire). Students attended a session prior to their internship that included information on background of the study, data collection methods, and instructions on how to conduct the interview. Students were instructed to wait for the technicians' answers and only prompt them with additional questions or examples when elaboration on initial answers was desired.

Analysis

The completed questionnaires were sent to the researchers. Answers were explored and categorised into groups by 2 researchers (DP and EF) independently. In case of inconsistencies a third researcher (EK) was consulted until consensus was reached.

Results

Thirty-one pharmacy technicians were interviewed. Not all technicians answered questions about their work experience; 89.5% (17 out of 19) of the technicians who gave this information had more than 5 years of experience, and 86.7% (26 out of 30) worked 32 hours a week or more. All technicians had counselled patients on problems with opening medicine packaging. The frequency of these consultations varied from once a year to twice a week. Two thirds (67.7%; n = 21) of the pharmacy technicians indicated that they encounter these problems at most once a month. According to the technicians, elderly patients (27 technicians) and patients with RA/other joint diseases (24 technicians) most commonly report packaging problems.

Problems with opening medicine packaging

Technicians have encountered patients who experience problems with 2 to 6 (out of 6 prompted) packaging forms (Table 1). In addition, 16 (72.7%) technicians describe problems with other (unprompted) packaging forms. Eighteen technicians (60.0%) stated that they do not always immediately know how to open a medicine packaging themselves, for example, for less common packaging forms or new medicines, but nearly all technicians are able to find out how to open the packaging. Eight pharmacy technicians actually tried to open the packaging themselves, and in one instance it is specified that this means the extracted tablet will be thrown away.

Solutions to problems with opening medicine packaging

Three categories of solutions to problems with opening packaging were examined: information and counselling, changing or manipulating the packaging, and suggesting or providing tools (Table 2). Most pharmacy technicians feel they can always offer an efficient solution, or that they think they could, if a problem is reported (82.1%, 23 technicians). Some say that they always try, but it might not always be possible (5 technicians). Reasons for this are that the technician may not be experienced enough, that it is not possible to change or manipulate the packaging for every patient (this is only done in exceptional cases), or that some patients refuse to pay for the assisting tools the pharmacy can offer.

Attention for problems with opening packaging in the pharmacy

Usually, attention for packages is reactive, and information or demonstrations are only given when patients bring up problems at the counter (20 technicians). Most pharmacy technicians state to only have structural attention for medicine packaging when it concerns a first (or second) dispensation of an uncommon dosage form, when switching to a generic, or when counselling is important for correct use (e.g., administration of inhalation medication; 17 technicians). Some also address opening of the packaging (or provide alternative packaging) proactively when there is a note in the patient's file about prior problems with opening the regular packaging, when dealing with specific patient groups (e.g., impaired patients in nursing homes), or when the technician is already aware of problems with opening that particular packaging (4 technicians). Two technicians would like to pay more attention to packaging and are willing to think about how this could be accomplished (e.g., putting up posters, offering multi-dose dispensing systems for certain patient groups). One technician noted that advising patients on how to open packages can be viewed as patronising (they expect negative reactions from patients, such as "I'm not stupid, I know how to open a bottle!"), and this is why they are reluctant. Another technician mentioned the lack of instruction from pharmacists on this subject, which leads to technicians using their own judgment in this matter.

Discussion

This study shows that every pharmacy technician encounters patients who have problems with medicine packaging. However, there is a wide range in the reported frequency of these encounters. Spontaneous reports of patients are rare in the pharmacy, although problems are not uncommon among patients.[8, 9] This suggests that medicine packaging is not systematically addressed during medication dispensation. Technicians usually only discuss the problems when patients bring them up themselves. Although it was only mentioned by a few technicians, insecurity with respect to counselling, sometimes caused by unclear protocols and procedures, could be part of the reason why they do not ask about experiences with the packaging, and why information on opening packaging is not systematically provided. Communication in the pharmacy might be hampered by a number of factors, such as lack of privacy and time constraints.[17, 18] Together with a possibly limited engagement of patients in communication on this topic, this could create a more passive and reactive (instead of proactive) attitude of technicians on this issue.[18] Another illustration of the importance of including the topic of medicine packaging in protocols and procedures is the great number of solutions related to manipulation of the packaging in the pharmacy (extracting tablets, unscrewing sealed caps, exchanging the original packaging for a more usable one). Manipulation introduces risks to the shelf-life of the medication when it is removed from the original packaging. Drawing up protocols that incorporate the experiences of technicians could improve commitment and confidence toward counselling, which could improve patient safety, medication adherence, and efficacy.

Strengths and limitations

This study gives insight into the perspective of the pharmacy technician on a subject that has not received a lot of attention. The method of data collection (semi-structured interviews) could have caused socially desirable answers. This could indicate that in daily practice there is even less attention for opening medicine packaging. This would further support our finding that attention to packaging is sporadic at best. Data collection was conducted by 31 different students, and although students had received clear instructions, there might be differences in the quality of the obtained data (e.g., variation in interview skills).

Practice implications

Discussing the packaging and asking about patients' experiences should become a fixed part of (first) dispensation counselling. Any first dispensation should include information on how to open the packaging, and for refill prescriptions counselling should involve asking patients about their experiences with opening the packaging and whether there were any problems. Especially elderly people and people with RA or other hand function limitations might

benefit from periodic monitoring. In addition, demonstrating how to open the packaging could help elucidate the difficulties and create an opportunity to provide tools for opening, or alternative packaging. Even though counselling in other countries may not be part of the work role of pharmacy technicians, studies conducted in other countries have also shown that opening packaging can cause problems for patients.[3-5, 7] These patients could benefit from systematically discussing the packaging at dispensation as well. Technicians exchanging knowledge and experience on specific problems and useful solutions could help create the most efficient and safe ways to assist patients on this issue. In addition, protocols or working procedures could be drawn up to support technicians in their counselling and should include the safest ways to manipulate the original packaging, when this is unavoidable.

Conclusion

This study shows that although pharmacy technicians are able to name a wide range of solutions to solve packaging problems, there is no systematic attention for packaging at drug dispensation in most pharmacies.

References

1. Knmp-richtlijn ter hand stellen [Royal Dutch Pharmacists Association Guideline Dispensation.]. 2013. Available from: http://www.knmp.nl/downloads/organisatie-regelgeving/organisatie-regelgeving-normen-en-richtlijnen/knmprichtlijn-ter-hand-stellen.
2. Atkin PA, Finnegan TP, Ogle SJ, Shenfield GM. Functional ability of patients to manage medication packaging: A survey of geriatric inpatients. Age Ageing. 1994;23(2):113-6
3. Beckman A, Bernsten C, Parker MG, Thorslund M, Fastbom J. The difficulty of opening medicine containers in old age: A population-based study. Pharm World Sci. 2005;27(5):393-8
4. Keram S, Williams ME. Quantifying the ease or difficulty older persons experience in opening medication containers. J Am Geriatr Soc. 1988;36(3):198-201
5. Lisberg RB, Higham C, Jayson MI. Problems for rheumatic patients in opening dispensed drug containers. Br J Rheumatol. 1983;22(2):95-8
6. Verheggen-Laming BN, Phiferons H, Mulder EF, van der Meij NT, van Harten RP, Dijkmans BA. Comparison of packages for suppositories by patients with rheumatoid arthritis. Scand J Rheumatol. 1988;17(3):161-5
7. Westerbotn M, Hilleras P, Fastbom J, Aguero-Torres H. Factors influencing the handling of medicines among very old people living at home in an urban area. Aging Clin Exp Res. 2006;18(6):497-502
8. van Geffen EC, Meuwese E, Philbert D, Bouvy ML. Problems with medicine packages: Experiences reported to a dutch medicine reporting system. Ann Pharmacother. 2010;44(6):1104-9
9. Philbert D, Notenboom K, Bouvy ML, van Geffen EC. Problems experienced by older people when opening medicine packaging. Int J Pharm Pract. 2014;22(3):200-4
10. van Hulten R, Blom L, Mattheusens J, Wolters M, Bouvy M. Communication with patients who are dispensed a first prescription of chronic medication in the community pharmacy. Patient Educ Couns. 2011;83(3):417-22
11. About the profession [National Pharmacy Technician Association]. Cited 2013 September 27. Available from: http://www.pharmacytechnician.org/en/cms/?831.
12. Alkhateeb FM, Shields KM, Broedel-Zaugg K, Bryan A, Snell J. Credentialing of pharmacy technicians in the USA. Int J Pharm Pract. 2011;19(4):219-27
13. Pharmacy technician: The job and what's involved [Input Youth]. Cited 2013 September 27. Available from: http://www.inputyouth.co.uk/jobguides/job-pharmacytechnician.html.
14. Pharmacy technician: Recognition of paramedical occupations—the pharmaceutical technical assistant (flyer) [paramedisch instituut. Apotheekassistent: Erkenning van paramedische beroepen—de farmaceutisch technisch assistent] [in dutch]. [Paramedical Institute]. Cited 2013 September 27. Available from: http://www.paramedin.be/images/documenten/infofolder_erkenning_fta_2010.pdf.
15. Competence profile pharmacy technician [competentieprofiel apothekersassistent] [in dutch] [Stichting Bedrijfsfonds Apotheken]. Cited 2013 February 21. Available from: http://www.sbaweb.nl/var/downloads/var/mediamanager/files/uploads/profiel_AA.pdf.
16. van Mil JW. Pharmaceutical care in community pharmacy: Practice and research in the netherlands. Ann Pharmacother. 2005;39(10):1720-5
17. van Geffen EC, Kruijtbosch M, Egberts AC, Heerdink ER, van Hulten R. Patients' perceptions of information received at the start of selective serotonin-reuptake inhibitor treatment: Implications for community pharmacy. Ann Pharmacother. 2009;43(4):642-9
18. Banks J, Shaw A, Weiss MC. The community pharmacy and discursive complexity: A qualitative study of interaction between counter assistants and customers. Health Soc Care Community. 2007;15(4):313-21

4.2

Chapter 4.2

In vitro disintegration and dissolution studies for the investigation of safe mixing of solid oral medicines with food to overcome swallowing problems

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Abstract

Up to one third of the general population finds it difficult to swallow solid oral medicines. The swallowing of intact tablets and capsules can be facilitated by co-administration with a spoonful of semi-solid food or a swallowing-gel. As this may affect the pharmacokinetics of a product, pharmaceutical companies should verify the impact of the co-administration on the safety and efficacy of a medicine in order to include such a recommendation in the product label. There are however no recognised in vitro methods for the investigation thereof. This study evaluated if pharmacopoeial in vitro disintegration and dissolution methods are suitable methods for the investigation of safe mixing of solid oral medicines with food. The effects of a small portion of applesauce, vanilla custard, yoghurt and an oral gel on the disintegration of carbamazepine tablets, dabigatran etexilate capsules, lithium carbonate immediate and prolonged release tablets and two different paracetamol tablets were investigated, as well as the effects of these vehicles on the dissolution of carbamazepine tablets. It is shown that co-administration of paracetamol, carbamazepine and lithium carbonate immediate release formulations with spoonful quantities of applesauce, vanilla custard, yoghurt and a gel lead to statistically significant and drug-dependent delays of tablet disintegration. In addition, it is shown that the co-administration of carbamazepine tablets with spoonful quantities of vanilla custard, yoghurt and gel lead to a statistically significant delay in dissolution. The findings suggest that in vitro testing can be used as an indicator of whether further investigations are warranted.

Introduction

Up to one third of the general population finds it difficult to swallow solid oral medicines, and these problems are even more common among older people.[1-4] The characteristics of the dosage form, such as its taste, surface texture, size and shape can present a challenge swallowing.[2, 3, 5] Physiological barriers for swallowing solid medicines are mouth dryness and dysphagia. A large number of medicines that are frequently prescribed to older patients cause dry mouth or dysphagia. Furthermore, swallowing disorders become more prevalent with increased age as they can be caused by age-related illnesses that affect the swallowing mechanism, such as Alzheimer's disease, Parkinson's disease, stroke and cancer.[6-8]

Common approaches to facilitate the swallowing of solid oral medicines are opening capsules, splitting, crumbling or crushing tablets, and mixing of the intact or altered dosage form with small or larger portions of food or drinks.[2, 3, 9, 10] Also, oral gels developed to aid the swallowing of medicines are available on the market. Such practices may affect the pharmacokinetics of the product. Either directly by interaction of the drug substance with the food or drink or indirectly by modifying the disintegration and dissolution process of the dosage form and drug substance, or by forming a physical barrier that prevents drug diffusion to the site of absorption. If not covered by the marketing authorisation, alternative administration methods are considered unlicensed use and therefore the responsibility of the health care professional or the user.

The European Medicines Agency (EMA) encourages the pharmaceutical industry to provide alternative administration strategies within the label of medicines intended for treatment in children.[11] Of course, such instructions could also be beneficial to other patient populations with problems with the administration of medicines. To support additional modes of administration, manufacturers should verify the impact on the safety and efficacy of the medicinal product. This may be done through specific bioavailability or bioequivalence studies with crushed or crumbled dosage forms mixed with small or larger portions of food or drinks.[11] Crushing or breaking of tablets is less appropriate among the older patient population as it demands a certain level of manual dexterity and strength.[12] For this population, studies with intact formulations seem more appropriate. However, it seems disproportionate to investigate all suggested additional modes of administration in human studies.

The EMA indeed points out that biostudies to support the co-administration with small portions of foods and drinks can be waived when existing information and/or in vitro studies on the influences of food provide sufficient justification of absence of a relevant effect of

the vehicle on the absorption of the active substance.[11] Standardised in vitro dissolution testing is already recognised by regulatory bodies for the assessment of the potential effect of concomitant intake of medicines with alcohol.[13] In vitro dissolution testing may also be suitable for the investigation of potential food-effects. Studying the additional modes of administration at an early phase of product development when it is still feasible to adapt the formulation seems recommendable. Yet, the investigation of effects of food and drinks by in vitro studies is not standard practice and is hampered by the absence of in vitro methods validated for this purpose.

In vitro disintegration and dissolution testing were previously described as suitable methods for predicting potential foods effects.[14-18] However, there is a limited number of publications addressing the effect of vehicles used as administration aid and the applied in vitro methodologies are not standardised. This study evaluated the effects of several vehicles on the disintegration and dissolution of intact solid oral dosage forms using standardised pharmacopoeial test methods. The aim was to evaluate if pharmacopoeial in vitro disintegration and dissolution methods are suitable screening tools for the investigation of safe and efficacious administration of intact solid oral dosage with small portions of food.

Material and methods

Medicinal products

Carbamazepine 200 mg tablets, Dabigatran etexilate 75 mg capsule, Lithium carbonate 200 mg tablets, Lithium carbonate 400 mg prolonged release tablets, Paracetamol 500 mg tablet, and Paracetamol 500 mg rapidly disintegrating tablets were selected. These six products represent solid oral dosage forms with different disintegration and drug release characteristics. The characteristics of the formulations are shown in Table 1.

The active substances are all highly permeable but exhibit different solubility characteristics, i.e. they belong to Class I or II of the Biopharmaceutic Classification System (BCS)[19-22]. The factors that control drug absorption for the selected products are thus the release of the active substance and/or dissolution from the dosage form. The medicinal products were purchased from a local pharmacy (Utrecht, the Netherlands). The medicinal products were stored according to their recommended storage conditions given on the packaging, and used before expiry date.

Vehicles

Applesauce, vanilla custard, yoghurt and a commercially available oral gel were chosen. Water was used as reference. The oral gel is a medical device developed to facilitate the

swallowing of solid medicines. It contains carrageen and other substances also used in food products. The instructions for use state that the medicine to be taken should be placed on a tablespoon, then covered with about 5 ml of the gel and next everything should be swallowed in one go.

The characteristics of the vehicles are presented in Table 2. The foods belonged to the private label of a local supermarket (Utrecht, the Netherlands). The gel was purchased from a local pharmacy (Utrecht, the Netherlands). The vehicles were stored according to their recommended storage conditions given on the packaging, and used before their expiry date.

Table 1 Characteristics of the medicinal products

Active substance and strength	BCS Class	Dosage form	Excipients
Carbamazepine 200 mg	II	Tablet	Colloidal anhydrous silica, microcrystalline cellulose, magnesium stearate, carmellose sodium (low-substituted)
Dabigatran etexilate 75 mg	II	Capsule, hard	Capsule: Carrageenan, potassium chloride, titanium dioxide, indigo carmine, sunset yellow, hypromellose, Capsule content: Tartaric acid, Acacia, hypromellose, dimeticon 350, talc, hydroxypropylcellulose Printing ink: Shellac, iron oxide black, potassium hydroxide
Lithium carbonate 200 mg	I	Tablet	Maize starch, gelatine, talc, gehydreerde ricinusolie
Lithium carbonate 400 mg	I	Modified release tablet	Glycerol palmitostearate, mannitol, acacia, sodium lauryl sulfate, magnesium stearate, maize starch, sodium starch glycolate
Paracetamol 500 mg	I	Film coated tablet	Maize starch, potassium sorbate, povidon K25, pregelatinised starch, stearic acid, talc Coating: Hypromellose, glycerol triacetate
Paracetamol 500 mg	I	Film coated tablet	Sodium bicarbonate, microcrystalline cellulose, pregelatinised maize starch, maize starch, magnesium stearate, povidone K25, potassium sorbate Coating: Carnaubawax, Opadry II Y-22-7719 white.

Table 2 Characteristics of the vehicles					
Vehicle (brand)	**Composition**	**pH**	**Fat**	**Protein**	**Viscosity [Pas]**
Applesauce	92% apple, sugar, citric acid, ascorbic acid	3.6	0.2 g/100 g	0.3 g/100 ml	0.580
Vanilla custard	Milk, whey, sugar, modified cornstarch, cornstarch, salt, aroma, colour (annatto), thickener	6.6	3.0 g/100 ml	2.0 g/100 ml	0.155
Yoghurt	Whole milk yoghurt, 0.4% milk protein	4.0	3.0 g/100 ml	4.0 g/100 ml	0.248
Gel	Carrageen, water, maltodextrin, calcium chloride, natural colourant, natural flavouring, aspartame, citric acid, potassium sorbate.	5.1	unknown	unknown	0.083

Materials for analytical procedures

European Pharmacopoeia (Ph.Eur.) Reference Standards of carbamazepine and carbamazepine Impurity A were purchased from the European Directorate for the Quality of Medicines (batch 5, both). Tetrahydrofuran, anhydrous formic acid, trimethylamine (all Merck), and methanol (Biosolve) used were of analytical grade. Purified water was used in the preparation of aqueous solutions.

Disintegration testing

Disintegration of the medicinal products was determined using a single basket tablet disintegration tester (Pharma Test PTZ-S, Germany) according to the Ph.Eur. (8th Ed) method 2.9.1. The test was carried out in 800 ml of demineralised water at 37 ± 2 °C. To mimic the intake of a dosage form with a vehicle, five millilitre of each vehicle was placed in a plastic tube, and a dosage unit was then placed in each tube. The contents of the tube were transferred to the disintegration beaker, directly after placing the dosage unit into tube. Three units were tested at the same time for each dosage form.

Dissolution testing

Carbamazepine 200 mg, immediate release tablets were selected as the model drug for dissolution testing. The dissolution method described in the U.S. Pharmacopoeial Convention (USP) monograph for carbamazepine 200 mg immediate release tablets was used. Five dissolution tests with carbamazepine were conducted; one with each vehicle (applesauce, vanilla custard, yoghurt and the gel), and a reference test with water as vehicle. Each test was performed in triplicate. To mimic the intake of a dosage form with a vehicle, five millilitre of each vehicle was placed in a plastic tube, and then one carbamazepine tablet was placed in each tube. The contents of the tubes were transferred to the dissolution medium in the

vessels, directly after placing the tablet into a tube. Dissolution profiles were generated in 900 ml of 1% sodium lauryl sulfate in water maintained at a temperature of 37±0.5°C, using USP Apparatus 2 (paddle method, Pharma Test PT-DT7, Germany) with paddle speed of 75 rpm. Four mL samples were withdrawn from the dissolution medium at 0, 5, 10, 15, 20, 30, 45, 60, 75, 90, 105 and 120 minutes, respectively, after starting the test. Samples were directly filtered through a 45-µm membrane. The drug release from the tablets was quantified using a validated HPLC method (as described below).

HPLC-analyses

High performance liquid chromatography (HPLC) method described in the British Pharmacopoeial monograph for assay of carbamazepine tablets was used to quantify the amount of carbamazepine dissolved in the samples from the dissolution tests. The analysis of the samples were carried out using Agilent Technologies 1200 series HPLC with DAD SL detector and HiP-ALS SL autosampler at ambient conditions, using stainless steel column (250 × 4.6 mm) packed with cyano (nitrile) modified silica for chromatography (5 µm, Nucleosil 5 CN) and mobile phase comprising tetrahydrofuran, methanol, water, anhydrous formic acid and trimethylamine (30:120:850:0.2:0.5) with a flow rate of 2 mL/min. System suitability testing showed a resolution of 3.5 between carbamazepine and carbamazepine Impurity A, and complied with the requirement of ≥ 1.7. The retention time of the drug was about 8.3 minutes. No matrix effects were observed caused by the presence of foods or gel.

Calculations and statistical analysis

Individual disintegration times were noted and the mean ±SD reported. Differences in tablet disintegration time between the tablets mixed with the different vehicles were tested for significance compared to water using one-way analysis of variance (ANOVA) followed by a multiple comparison post hoc test (Dunnet). Data were analysed using SPSS software version 22 (SPSS Inc., Chicago, IL, USA). The results were considered statistically significant when $P < 0.05$.

For dissolution testing, the cumulative percentages of drug dissolved from the tablets were calculated. The volume withdrawn by sampling was corrected for by calculation. Dissolution profiles were created upon the mean percent of drug dissolved. To compare the dissolution profiles, similarity factors (f2) were calculated by using the following formula:

$$f2 = 50 \times \log\left\{\left[1 + (1/n)\sum(Rt - Tt)^2\right]^{-0.5} \times 100\right\} t = 1$$

In this equitation f2 is the similarity factor, n is the number of time points, Rt is the mean percent drug dissolved without mixing at time t after initiation of the study; Tt is the mean percent drug dissolved mixed with one of the foods or the gel at time t after initiation of the study. An f2 value between 50 and 100 suggests that the two dissolution profiles are similar.[23] All calculations were performed in MS Excel.

Results

Disintegration testing

The mean disintegration times of the tablets in water varied between 40 seconds for carbamazepine immediate release tablets and almost 30 minutes for the lithium carbonate prolonged release tablets. The mean disintegration times of the products in the reference medium and following mixing with the vehicles are compared in Table 3. The one-way analysis of variance revealed significant differences between the disintegration times of the immediate release products in water or mixed with the vehicles ($P<0.05$, for all immediate release products). No significant effect of the vehicles on the disintegration time of the prolonged release tablet was observed ($P=0.649$). Post hoc comparisons using Dunnet test revealed that yoghurt and gel significantly delayed the disintegration time of carbamazepine tablets ($P=0.039$ and $P=0.024$, respectively) and lithium immediate release tablets ($P=0.001$ and $P<0.001$, respectively), compared to disintegration time in water.

The disintegration time for the carbamazepine tablets was prolonged up to 1.5 times by yoghurt and gel (from 40 to approx. 60 seconds for both products) and the disintegration time of lithium immediate release tablets up to 4 times (from 42 to 165 and 186 seconds, respectively). Vanilla custard significantly delayed the disintegration time of the two different paracetamol tablets ($P=0.007$ for the rapidly disintegrating tablets, $P=0.013$ for the regular tablets) and the lithium immediate release tablets ($P<0.001$). The disintegration time of rapidly disintegrating paracetamol tablets was delayed by 1.5 times when mixed with vanilla custard (from 232 to 369 seconds), by more than 2 times for regular paracetamol tablets (from 566 to 1309 seconds) and by more than 7 times for the immediate release lithium tablets (from 42 to 300 seconds), compared to that in water.

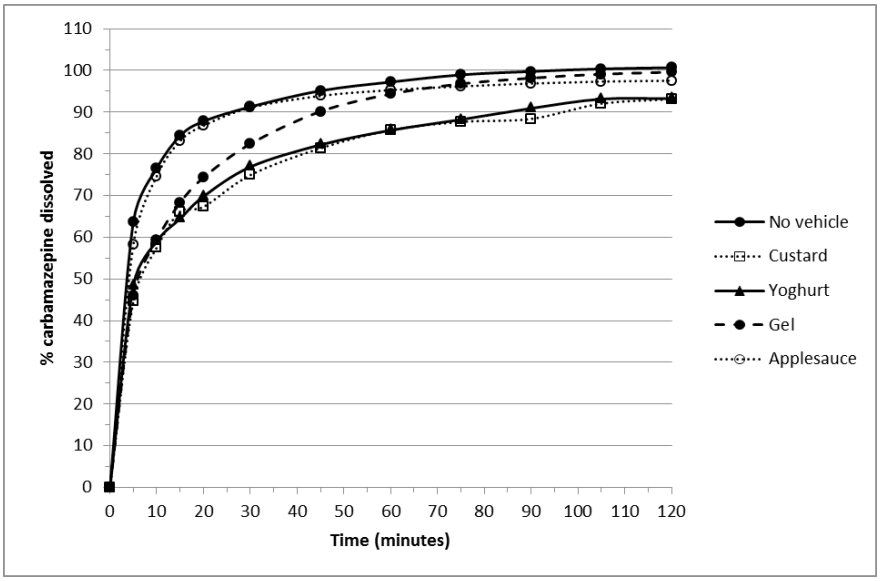
Table 3 Mean disintegration time for the investigated tablets in the vehicles (*n*=3)					
	Mean (sd) disintegration time in seconds				
Medicinal product	**Water**	**Applesauce**	**Vanilla custard**	**Yoghurt**	**Gel**
Carbamazepine 200 mg, tablet	40.33 (2.9)	58.33 (5.5)	57.00 (-)[#]	60.67* (15.5)	62.67* (7.5)
Dabigatran etexilate 75 mg, capsule, hard	173.67 (37.3)	227.67* (13.3)	180.0 (-)[#]	176.67 (5.8)	200.33 (24.1)
Lithium carbonate 200 mg, tablet	42.33 (4.9)	107.33 (12.9)	299.67* (59.6)	180.00* (15)	185.67* (13.6)
Lithiumcarbonaat 400mg, modified release tablet	1777.33 (5.5)	1835.33 (33.5)	1821.33 (97.5)	1770.00 (68.8)	1776.33 (76.4)
Paracetamol 500 mg, film coated tablet	566.33 (93.6)	680.67 (184.5)	1309.00* (436.8)	549.33 (22.5)	836.00 (251.8)
Paracetamol 500 mg, film coated tablet (rapidly disintegrating)	231.67 (23.1)	254.00 (30.2)	369.33* (68.3)	301.00 (43.5)	268.00 (22.0)

* $P < 0.05$, statistically significant from water as vehicle.
[#] limit test used, due to poor visibility.

Dissolution testing

The rate of in vitro dissolution of the immediate release carbamazepine tablets in the presence of the oral gel, applesauce, yoghurt and vanilla custard was investigated in comparison to the absence of these vehicles. The dissolution data is presented in Table 4, whereas comparative dissolution profiles are shown in Figure 1. The release of carbamazepine in the presence of applesauce was similar to the release in the absence of a vehicle and relatively fast, i.e. more than 85% of the carbamazepine was dissolved in 20 minutes. Dissolution was delayed to more than 85% dissolved in 45 minutes for the tablets mixed with gel, and to more than 85% dissolved in 60 minutes for the tablets mixed with yoghurt or vanilla custard. The f2-values for carbamazepine in the presence of applesauce, gel, yoghurt and vanilla custard when compared to the absence of a vehicle were 75.1, 39.6, 37.5 and 35.8, respectively. For all media, the current USP recommendations were met (45-75% dissolved within 15 minutes and not less than 75% dissolved in 60 minutes).

Figure 1 **Comparative dissolution time profiles in 1% SLS1 of carbamazepine 200 mg immediate release tablets mixed with 5 ml of the investigated vehicles and without vehicle**



[1] Test method and conditions as described in the USP monograph for carbamazepine 200 mg tablets.

Table 4 **The percentage dissolution (mean and relative standard deviation (RSD) in 1% SLS[1] for carbamazepine 200 mg immediate release tablets mixed with 5 ml of the investigated vehicles and without vehicle**

	Carbamazepine dissolved, mean % (RSD)				
Time point	**No vehicle**	**Applesauce**	**Vanilla custard**	**Yoghurt**	**Gel**
5 min	63.68 (4.39)	58.23 (1.02)	44.61 (4.76)	48.47 (5.20)	46.08 (10.24)
10 min	76.51 (2.95)	74.66 (2.25)	57.52 (8.27)	59.03 (4.86)	59.38 (10.06)
15 min	84.33 (3.04)	83.10 (1.88)	66.15 (10.64)	64.47 (1.63)	68.27 (8.51)
20 min	87.80 (0.73)	86.75 (1.51)	67.28 (7.75)	69.78 (4.31)	74.30 (5.15)
30 min	91.28 (1.08)	91.07 (1.23)	74.91 (8.32)	76.88 (0.71)	82.40 (3.71)
45 min	95.13 (1.35)	93.90 (0.49)	81.35 (6.33)	82.16 (1.36)	90.17 (0.81)
60 min	97.23 (0.85)	95.30 (0.85)	85.69 (4.60)	85.65 (5.15)	94.35 (0.51)
75 min	98.95 (0.58)	96.19 (1.06)	87.66 (7.06)	88.21 (0.51)	96.79 (1.27)
90 min	99.76 (0.36)	96.88 (1.11)	88.39 (3.74)	90.92 (0.91)	98.18 (1.64)
105 min	100.39 (0.37)	97.34 (1.46)	92.05 (6.69)	93.15 (1.13)	99.12 (1.80)
120 min	100.67 (0.39)	97.54 (1.38)	93.09 (3.02)	93.24 (1.50)	99.59 (1.89)
f_2 value	-	75.1	35.8	37.5	39.6

1 Test method and conditions as described in the USP monograph for carbamazepine 200 mg tablets.

Discussion

The swallowing of intact tablets and capsules can be facilitated by co-administration with a spoonful of semi-solid food or a swallowing-gel. This study evaluates the effects of small portions of foods on dissolution and disintegration of solid oral dosage forms by use of pharmacopoeial test methods. Carbamazepine and lithium carbonate immediate release tablets were the most sensitive to a delay in disintegration time caused by the vehicles, which could be related to the absence of a film-coat. In addition, it is shown that the co-administration of carbamazepine tablets with spoonful quantities of vanilla custard, yoghurt and gel lead to a statistically significant delay in dissolution. The disintegration for dabigatran etexilate capsules in the presence of yoghurt and custard was comparable to that of water.

The compendial disintegration test visually monitors the time necessary for a dosage form to break up into particles under standardised conditions. The disintegration time of a dosage form is predominantly determined by wetting of the dosage form and liquid penetration into its pores. These processes are influenced by dosage form related factors, such as its composition, e.g. types and quantities of binders, disintegrants and lubricants, type of capsule shell, e.g. hydroxypropyl methylcellulose or gelatine, presence and type of coating and tablet hardness. Dosage forms that do not fully disintegrate or disintegrate only slowly may fail to release the drug substance completely within the absorption window, resulting in reduced dissolution and bioavailability of the active substance. Disintegration testing is widely used during product development with the purpose of optimising the formulation. Besides (internal) dosage form related factors, also the (external) presence of co-administrated food can impede wetting and liquid penetration, and may physically prevent particles leaving the dosage form. These food effects can be explained by the precipitation of a (protein) film on the tablet surface[14, 24] and/or increased media viscosity.[25, 26]

The effects of both dosage form related factors and external factors on the disintegration time of a dosage form can be measured by the compendial disintegration test. The physiological relevance of this test is often questioned due to the use of a non-biorelevant medium (water) and a high mechanical agitation level. However, Abrahamsson et al. showed the presence of a protein film-layer around tablets while using the compendial disintegration method.[14] The biorelevance of this film-layer was demonstrated by an in vivo study in dogs during which administered tablets were removed through a gastric fistula, which showed that the delay on tablet disintegration caused by the film and as found in vitro, persisted in vivo. Hence, the protein film as formed in the disintegration test appears not to be affected in vivo by enzymes or other physiological factors not included in the disintegration model.

A practical drawback of the compendial disintegration test is the visual determination of time to disintegrate. Depending on the foods used, it may be difficult to determine if and when the dosage form is fully disintegrated because the food impedes the visibility. In the current study, the effects of vanilla custard on disintegration of carbamazepine and dabigatran could not be properly determined due to the poor visibility caused by the custard. Another drawback of the disintegration method is that disintegration does not imply complete dissolution of the active substance as required for absorption. Dosage forms that show acceptable disintegration can still exhibit poor dissolution. Hence, the disintegration test cannot be solely relied upon while investigating the effects of co-administration with food. Disintegration testing can however provide insight into the cause of dissolution changes.

Dissolution testing is performed to measure the amount of drug substance that dissolves in the medium per unit time under standardised conditions. Dissolution testing encompasses disintegration of the dosage form, the release of the drug substance particles and dissolution of the particles into the medium. As for disintegration testing, the predictability of in vivo behaviour is generally limited, as in vitro dissolution studies do not simulate the physiological environment, e.g. solubilising agents like bile salts, gastric emptying rate and transit time. These factors may significantly affect in vivo dissolution, and consequently drug absorption and bioavailability. Over the last decades, researchers aimed to increase the in vivo predictability of in vitro dissolution testing. This included the establishment of validated In Vitro In Vivo correlations (IVIVC) and the development of biorelevant dissolution media. However, up to now regulatory bodies have only accepted standardised in vitro dissolution studies using buffers within the physiological range to waive biostudies and to a limited extent IVIVC correlations. We selected carbamazepine immediate release tablets as a model drug to study the effects of the foods and gel on dissolution. Dissolution is the rate-limiting step in the absorption of carbamazepine immediate release tablets. The substance has a very low solubility (113 µg/mL, 25°C) and high permeability, and is categorised as a BCS class II agent. We used the USP dissolution method for carbamazepine 200 mg immediate release tablets. For this method a level C in vitro/in vivo correlation has been established for the carbamazepine tablets used in our study. A relationship between Cmax and the % carbamazepine dissolved in vitro was determined at 20, 40 and 50 minutes, and it was found that Cmax was best predicted by the percentage dissolved at 20 minutes (D20). On the basis of the IVIVC results between D20 and Cmax found, and the requirements for bioequivalence (AUC0-∞: 0.8±1.25 and Cmax; 0.75- 1.35; 90% coincidence interval) the following dissolution rate specification was set `after 20 min, 34±99% dissolved' [27, 28]. The results of the current study show that mixing carbamazepine immediate release tablets with spoonful quantities of gel, yoghurt and custard delayed the dissolution of carbamazepine, resulting in dissimilar dissolution profiles compared to the dissolution in the absence of food or gel. No effect

on the dissolution was found following mixing the tablets with applesauce. The effects of yoghurt and custard on dissolution were similar, and stronger than the effect of the gel. Taking into account the dissolution results after 20 min (see Figure 1), it can be deduced that the dissolution results of carbamazepine co-administered with all vehicles complied with the specification, as well as with the current USP dissolution requirements (45-75% dissolved in 15 minutes and not less than 75% in 60 minutes). It is therefore not expected that the delayed dissolution by these small portions of food and gel will delay the rate of absorption of carbamazepine or otherwise affect carbamazepine plasma concentration profiles to a clinically relevant extent.

The findings of this study show that the compendial disintegration method and the compendial dissolution method for carbamazepine tablets were both capable of demonstrating effects of small quantities of food and gel on the behaviour of carbamazepine tablets. The effects of the vehicles on the carbamazepine dissolution profiles are reflected by the findings of the disintegration study; both showing a statistical significant effect of yoghurt and gel. Custard has a similar effect on the dissolution of carbamazepine as yoghurt, but its effect on the disintegration time was difficult to determine due to the problematic visibility. The need for proper visibility in the test medium makes disintegration testing less suitable for the screening of potential food effects. Potential reasons for the effects of custard and yoghurt could be the formation of a protein film-layer, as demonstrated by Abrahamsson et al.[14] This does however not clarify the observed effects for the co-administration with gel. Other aspects that play a role are, amongst others, viscosity, time that the food and dosage form remain in contact with each other and characteristics of the dosage form such as surface area and presence of a film-coat. During the conduct of the in vitro studies it was clearly visible that the applesauce rapidly immersed in the media used for the in vitro testing, whereas the custard, yoghurt and the gel remained in contact with the tablets for a longer period of time. Our study is however too limited to determine the exact effect of the multifaceted process of the effects of food on disintegration and dissolution properties of dosage forms.

The calculation of f2 factor based on the dissolution profile leads to overdiscriminatory conclusions. This could be concluded as an IVIVC for the same method is available and the dissolution profile remains within the range for which bioequivalence was demonstrated. The application of an overdiscriminatory tool can be useful during product development to decide on the need for further investigations: for those formulations that do not show an effect at overdiscriminatory conditions it can be concluded that no additional research is needed, while for those that do show an effect the conduct of additional in vitro or in vivo studies would seem appropriate. The applied dissolution conditions were appropriate for the testing of carbamazepine tablets, especially in view of the available IVIVC. Other

dissolution conditions may be used for products for which no IVIVC has been established, e.g. dissolution at three physiological pH levels, which is commonly applied for the evaluation of the effects of concomitant intake of solid oral dosage forms with alcohol. Previous studies suggest that these conditions can also be used for the evaluation of food effects.[15, 18]

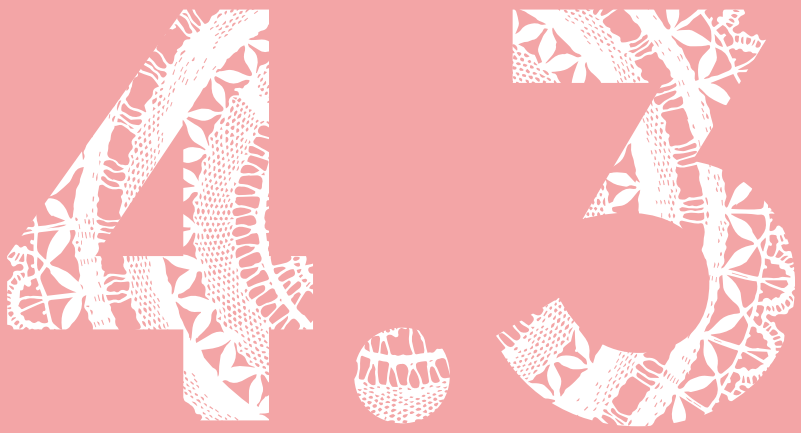
Conclusions

Difficulties with the swallowing of medicines become more relevant as the average population age increases, and hence the need for additional administration instructions for tablets and capsules becomes more relevant too. Appropriate in vitro screening tools to evaluate potential incompatibility issues with foods or other vehicles used for co-administration of medicines will facilitate the inclusion of alternative administration techniques within the product label. This study suggests that in vitro testing is likely to predict whether further investigations, e.g. biostudies, are warranted. However, more dissolution data, with drug products exhibiting different disintegration and drug release properties, would be necessary. We used a product for which an IVIVC was established by Lake et al. previously. In the absence of an IVIV-correlation, in vitro findings could have triggered for further in vivo evaluation. Hence, further studies are needed to investigate the in vivo significance of the in vitro findings. Clinical investigators are encouraged to contribute to the development of in vitro screening tools by conducting in vitro studies parallel to in vivo studies.

References

1. Andersen O, Zweidorff OK, Hjelde T, Rodland EA. [problems when swallowing tablets. A questionnaire study from general practice]. Tidsskr Nor Laegeforen. 1995;115(8):947-9
2. Schiele JT, Quinzler R, Klimm HD, Pruszydlo MG, Haefeli WE. Difficulties swallowing solid oral dosage forms in a general practice population: Prevalence, causes, and relationship to dosage forms. Eur J Clin Pharmacol. 2013;69(4):937-48
3. Marquis J, Schneider MP, Payot V, Cordonier AC, Bugnon O, Hersberger KE*, et al.* Swallowing difficulties with oral drugs among polypharmacy patients attending community pharmacies. Int J Clin Pharm. 2013;35(6):1130-6
4. Liu F, Ranmal S, Batchelor HK, Orlu-Gul M, Ernest TB, Thomas IW*, et al.* Patient-centred pharmaceutical design to improve acceptability of medicines: Similarities and differences in paediatric and geriatric populations. Drugs. 2014;74(16):1871-89
5. Liu F, Ghaffur A, Bains J, Hamdy S. Acceptability of oral solid medicines in older adults with and without dysphagia: A nested pilot validation questionnaire based observational study. Int J Pharm. 2016
6. Serra-Prat M, Hinojosa G, Lopez D, Juan M, Fabre E, Voss DS*, et al.* Prevalence of oropharyngeal dysphagia and impaired safety and efficacy of swallow in independently living older persons. J Am Geriatr Soc. 2011;59(1):186-7
7. Kawashima K, Motohashi Y, Fujishima I. Prevalence of dysphagia among community-dwelling elderly individuals as estimated using a questionnaire for dysphagia screening. Dysphagia. 2004;19(4):266-71
8. Holland G, Jayasekeran V, Pendleton N, Horan M, Jones M, Hamdy S. Prevalence and symptom profiling of oropharyngeal dysphagia in a community dwelling of an elderly population: A self-reporting questionnaire survey. Dis Esophagus. 2011;24(7):476-80
9. Notenboom K, Beers E, van Riet-Nales DA, Egberts TC, Leufkens HG, Jansen PA*, et al.* Practical problems with medication use that older people experience: A qualitative study. J Am Geriatr Soc. 2014;62(12):2339-44
10. Stubbs J, Haw C, Dickens G. Dose form modification - a common but potentially hazardous practice. A literature review and study of medication administration to older psychiatric inpatients. Int Psychogeriatr. 2008;20(3):616-27
11. Guideline on pharmaceutical development of medicines for paediatric use, EMA/CHMP/QWP/805880/2012 Rev. 2. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) & Paediatric Committee (PDCO) (2013).
12. Notenboom K, Vromans H, Schipper M, Leufkens HG, Bouvy ML. Relationship between age and the ability to break scored tablets. Front Pharmacol. 2016;7:222
13. Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms, EMA/CPMP/EWP/280/96 Corr1. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) (2014).
14. Abrahamsson B, Albery T, Eriksson A, Gustafsson I, Sjoberg M. Food effects on tablet disintegration. Eur J Pharm Sci. 2004;22(2-3):165-72
15. Cvijic S, Parojcic J, Langguth P. Viscosity-mediated negative food effect on oral absorption of poorly-permeable drugs with an absorption window in the proximal intestine: In vitro experimental simulation and computational verification. Eur J Pharm Sci. 2014;61:40-53
16. Carrier MN, Garinot O, Vitzling C. Stability and compatibility of tegaserod from crushed tablets mixed in beverages and foods. Am J Health Syst Pharm. 2004;61(11):1135-42
17. Manrique YJ, Lee DJ, Islam F, Nissen LM, Cichero JA, Stokes JR*, et al.* Crushed tablets: Does the administration of food vehicles and thickened fluids to aid medication swallowing alter drug release? J Pharm Pharm Sci. 2014;17(2):207-19
18. Wells KA, Losin WG. In vitro stability, potency, and dissolution of duloxetine enteric-coated pellets after exposure to applesauce, apple juice, and chocolate pudding. Clin Ther. 2008;30(7):1300-8
19. Pradaxa: Epar - public assessment report: European Medicines Agency (EMA); 2008; Cited 2016 01-12-12016. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000829/human_med_000981.jsp&mid=WC0b01ac058001d124.

20. Who expert committee on specifications for pharmaceutical preparations. Fortieth report. World Health Organ Tech Rep Ser. 2006;937:1-461
21. Hhs/fda guidance for industry.: Dissolution testing of immediate release solid oral dosage forms. Rockville, MD: U.S. Department of Health and Human Service Food and Drug Administration; 1997.
22. Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system. Center for Drug Evaluation and Research (CDER); 2015.
23. Guideline on the investigation of bioequivalence, CPMP/EWP/QWP/1401/98 Rev. 1/ Corr. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) (2010).
24. Kalantzi L, Polentarutti B, Albery T, Laitmer D, Abrahamsson B, Dressman J*, et al.* The delayed dissolution of paracetamol products in the canine fed stomach can be predicted in vitro but it does not affect the onset of plasma levels. Int J Pharm. 2005;296(1-2):87-93
25. Parojcic J, Vasiljevic D, Ibric S, Djuric Z. Tablet disintegration and drug dissolution in viscous media: Paracetamol ir tablets. Int J Pharm. 2008;355(1-2):93-9
26. Radwan A, Amidon GL, Langguth P. Mechanistic investigation of food effect on disintegration and dissolution of bcs class iii compound solid formulations: The importance of viscosity. Biopharm Drug Dispos. 2012;33(7):403-16
27. Lake OA, Olling M, Barends DM. In vitro/in vivo correlations of dissolution data of carbamazepine immediate release tablets with pharmacokinetic data obtained in healthy volunteers. Eur J Pharm Biopharm. 1999;48(1):13-9
28. Olling M, Mensinga TT, Barends DM, Groen C, Lake OA, Meulenbelt J. Bioavailability of carbamazepine from four different products and the occurrence of side effects. Biopharm Drug Dispos. 1999;20(1):19-28


4.3

Chapter 4.3

Breaking bad: predicting the performance of score marks

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Abstract

Reported problems with breaking scored tablets concern the reliability of score marks and consequentially, of fractional dosing. A predictive model for the ease of breaking scored tablets has been developed previously. The model is based on the association between the physical characteristics of scored tablets and the actual ease of breaking for these tablets obtained by a test panel, and predicts the proportion of people that would break a specific tablet. The present study aims to investigate the performance of the predictive model in real clinical practice. We measured the ease of breaking of eleven scored tablets using a test panel, and expressed the outcome as the fraction of the 36 participants that was able to break each specific tablet. The findings were compared with the predicted proportion of people able to break each tablet. The results show that the observed and predicted findings do not correspond well. The unsatisfactory predictive ability is explained by differences between the two studies, as well as the small sample size used for model development and confounded variables. We recommend to update the predictive model regarding these points. Furthermore, we advise that manufacturers rationalise tablet geometry with respect to shape, size and depth of the score mark.

Introduction

The presence of a score mark or score marks on a tablet enables customising a dose to individual needs. Score marks help to achieve doses that are not commercially available, such as the lower doses often needed to treat children or older people. In addition, score marks may facilitate breaking for ease of swallowing. Problems with breaking tablets, such as difficulty with breaking or breaking in uneven parts and loss of mass have been reported several times. These issues raise concerns on the reliability of score marks and consequentially, of fractional dosing. Besides fluctuations in the administered dose, bad score mark performance may have negative consequences on patient compliance with drug regimens, as patients may skip or double doses rather than breaking tablets.[1-18]

Whereas score marks should facilitate both the ease and the accuracy of breaking, the current European standard for the performance of score marks assesses only the accuracy of breaking. Furthermore, the standard defines no characteristics of the person performing the test for accuracy of breaking.[19] Consideration needs to be given to the ease of breaking when evaluating the performance of score marks. Also, the capabilities of the intended user population of the medicinal product need to be taken into account. Our previous study demonstrates that in comparison to young adults, older people more frequently experience difficulties with the ease of breaking tablets. On average, the older adults were able to break 38.1% of the tablets presented to them, whereas the young adults broke 78.2% of the tablets.[20]

Several studies identified physical characteristics of tablets that are associated to the ease of breaking, e.g. the shape, thickness and diameter of the tablet and the depth of the score mark.[9, 13] Moreover, a predictive model for the ease of breaking that includes physical characteristics of tablets has been developed previously. The model was developed for round scored tablets, using outcomes for actual ease of breaking obtained by a test panel. Within the same study, criteria for physical characteristics of oblong scored tablets were established that would ensure their sufficient ease of breaking. The researchers concluded that the predictive model for round scored tablets and the criteria for oblong tablets are sufficiently reliable for use during product development.[21] There is, however, limited evidence for how well the model and criteria perform in predicting the ease of breaking in real clinical practice. Therefore, the present study aims to investigate the predictive performance of both the model for round tablets and the criteria for oblong tablets by comparing the predicted breaking ease with actual outcomes in a test panel.

Material and methods

Tablets

Eleven commercially available tablets were included in the study: nine round scored tablets and two oblong scored tablets. All tablets were purchased during a previous study in which there ease of breaking by a test panel was evaluated.[20] Information on the type of score mark (standard or pressure sensitive) and presence of a film-coating were taken from the Summary of Product Characteristics and the MA-holders' website. The score form (score line or score cross), score mark (one- or two-sided presence of the score mark), the shape (round, oblong) and surface shape (biconvex or flat) of a tablet were visually determined. Diameter, length, width, and thickness of the tablets were measured with a calibrated digital vernier caliper. The tablets were weighed to the nearest 0.0001g using a Mettler Toledo AT201 analytical balance. Resistance to crushing was determined according to the method described in the European Pharmacopeia.[22]

Predicted ease of breaking

The ease of breaking the round scored tablets is predicted based on their physical characteristics using the model developed by Van der Steen et al.[21] The model is based on the association between the physical characteristics of 20 different round scored tablets and the actual ease of breaking for these 20 tablets obtained by a test panel of about 22 older people. In other words, the predicted ease of breaking predicts the proportion of people that would be able to break a specific tablet. The development of the model involved model building using logistic regression analysis based on the training set of 20 tablets, internal validation of the model using boot strap techniques, evaluation of discriminative ability (C-index) and external validation by five tablets that were not part of the training set but broken by the same test panel. The characteristics included in the final model are, in decreasing order of importance, resistance to crushing, diameter, score mark (one- or two-sided), thickness and shape (flat or biconvex). The oblong tablets are assessed for compliance with criteria that were established by the same researchers. When an oblong tablet complies with these criteria, it is predicted that at least 80% of the people is able to break the specific tablet.[21] The model for round tablets and the criteria for oblong tablets are shown in Figure 1.

Ease of breaking by a test panel

The data for the ease of breaking were taken from our previous study in which a test panel of 36 older people were scored on their ability to break tablets by three common techniques for breaking tablets by hand: breaking in between the fingers with the use of nails, breaking in between the fingers without the use of nails and pushing the tablet downward with one

finger on a solid surface (Figure 2). The ease of breaking of the tablets is expressed as the fraction of the 36 participants that was able to break the specific type of tablet by at least one of the methods.[20]

Figure 1 Prediction of the ease of breaking of scored tablets from their physical parameters[21]

Round tablets

The predicted proportion of participants that is able to break the tablet is:

expit* [-1.56 – (0.05 x resistance to crushing (N)) + (1.04 x diameter (mm)) + (5.16 x score mark (one – side = 0; two-sided = 1)) – (0.82x) thickness(mm)) – (0.90 x shape (biconvex = 0; flat = 1))]

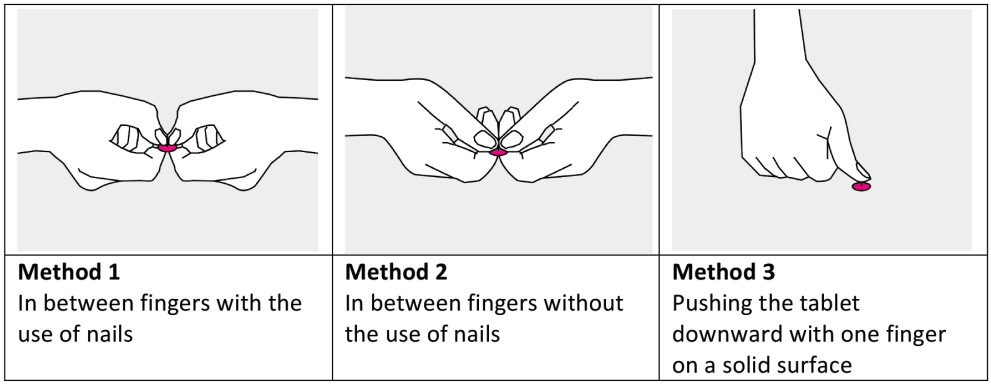
Oblong tablets

The predicted proportion of participants that is able to break the tablet is ≥ 0.800 when:

Diameter is ≥ 10 mm; AND diameter/width ratio is ≥ 2.0; AND depth of score line is ≥ 0.5 mm; AND resistance to crushing is ≤ 100 N

* expit(x) =ex/(1+ex)

Figure 2 The three methods for breaking scored tablets by hand



Method 1 In between fingers with the use of nails	**Method 2** In between fingers without the use of nails	**Method 3** Pushing the tablet downward with one finger on a solid surface

Results

The physical characteristics of the eleven tablets, the observed ease of breaking by the test panel and the predicted ease of breaking are presented in Table 1. The results show that the observed and predicted findings do not correspond well. For three tablets, tablet C1, C2 and D1, the difference between the predicted and actual proportion of participants able to break the tablet is 6.1%, 2.3% and 8.7%, respectively, but for the other six round tablets the

Table 1. **Physical characteristics of the eleven tablets included in this study and the outcomes for predicted ease of breaking and the ease of breaking by the test panel**

Code	A1	A2	A3	B1	B2	B3	C1	C2	D1	D2	D3
Mass (mg)	90	181	182	185	137	182	172	93	250	237	320
Shape (round/ oblong)	Round	Round	Round	Round	Oblong	Round	Round	Round	Round	Oblong	Round
Shape (flat/biconvex)	Biconvex	Biconvex	Biconvex	Biconvex	Biconvex	flat	Biconvex	Biconvex	Biconvex	Biconvex	flat
Filmcoated	Yes	No	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Diameter or length (mm)	5.70	7.61	7.63	8.00	8.18	8.16	7.10	6.54	9.15	11.58	10.22
Width (mm)	-	-	-	-	5.64	-	-	-	-	6.38	-
Diameter/width ratio	-	-	-	-	1.45	-	-	-	-	1.82	-
Thickness (mm)	2.50	3.93	3.93	3.84	3.74	3.30	3.72	2.69	3.94	3.85	3.91
Score type	Pressure	Standard	Standard	Pressure	Standard	Standard	Pressure	Standard	Pressure	Standard	Standard
Score form	Cross	Line	Line	Line	Line	Line	Line	Line	Line	Line	Line
Score mark (one-/two- sided)	One	One	One	One	One	Two	One	One	One	One	Two
Resistance to crushing (N)	12	5	5	55	73	138	6	7	63	50	128
Predicted ease of breaking	0.693	0.879	0.881	0.490	≤ 0.800	0.923	0.828	0.856	0.663	≤ 0.800	0.990
Proportion broken by test panel	0.500	0.611	0.556	0.083	0.639	0.306	0.889	0.833	0.750	0.833	0.639

predicted ease of breaking deviated from the findings by the test panel by approximately 20-60%.

In addition, the established criteria for sufficient ease of breaking of oblong scored tablets, defined by the previous study as more than 80% of the participant being able to break the tablets, are not confirmed. Both tablet B2 and D2 did not comply with the criteria that predict sufficient ease of breaking, whereas it was observed that tablet D2 was broken by about 83% of the participants. Tablet B2 was broken by 64% of the participants.

Discussion

Round tablets

The model's ability to predict the proportion of people able to break a specific tablet in clinical practice is unsatisfactory. There are several possible explanations for the dissimilar findings for the predicted and the actual observed ease of breaking, including differences between the tablets, the study settings and participants, but also the sample size and confounding variables used for the development of the model provide a clarification.

The training set of 20 different tablets is relatively small in view of all possibilities for tablet characteristics that are available on the market, which could adversely affect the model's performance as the small training-sample makes that the model needs to extrapolate beyond the extremes of the tablet characteristics. Also, the variables 'resistance to crushing' and 'score type', i.e. one-sided or two-sided, may be confounded. The variable 'score type', i.e. the presence of a one- or two-sided score mark, is considered confounded due to the fact that the training set of 20 round tablets included only one tablet with a two-sided score mark and none of the five samples for the test set had a double sided score. The only tablet with the double sided score mark also shows other extreme values: it is the thickest tablet of the sample (4.6 mm), shows the highest value for resistance to crushing (206.0 N), has the second largest diameter (11.0 mm) and one of the lowest in vivo ease of subdivision (0.476). This tablet therefore has a large influence on the model. Resistance to crushing is the most critical parameter of the model. However, the values for resistance to crushing of the tablets included in the training and the test set were obtained in two different ways and are therefore not fully comparable. For 18 of the 20 tablets of the training set the resistance to crushing was measured according to the method described in the European Pharmacopeia, whereas for all five tablets of the test set, the resistance to crushing was obtained from their marketing authorisation file, i.e. from the process validation results, release specification or stability data. In general, the resistance to crushing is presented as

a range in the marketing authorisation files and not as a fixed value. This range can be quite wide, e.g. the resistance to crushing stated in the marketing authorisation dossiers for the tablets of our sample, if available, are: tablet A1 30-90 Newton, B2 60-110 Newton (prior to coating), C1 ≤ 40 Newton, C2 40-160 Newton and tablet D3 ≥ 60 Newton. Sometimes, the criteria for resistance to crushing applied for stability testing are wider than those applied for release testing because this parameter is known to decrease during storage. It is unclear what values were taken from the marketing authorisation dossiers, e.g. average, highest or lowest acceptable value. Furthermore, values obtained from the dossier cannot be regarded as similar to those actually measured because the derived values for resistance to crushing are influenced by the testing conditions, such as tablet orientation, type of tester used and its electronics, and settings for speed and force.

Differences between the participants and the setting of the previous study and the current study could also explain the unsatisfactory predictive performance of the model. As it is impossible to use the same participants as the previous study, we kept participant characteristics with regard to in- and exclusion criteria, living circumstances and age distribution similar. The members from both panels were recruited for homes for the elderly in Utrecht, The Netherlands. The mean age of the participants of the test panel used for model development was 83 years (range 71-95), and that of the current test panel was 84.2 years (range 69-97 years). Individuals with impaired use of hands and/or fingers were excluded. The small difference in gender ratio between the panels (22-24% males in the previous test panel versus 31% males in the current test panel) is not considered to clarify the poor performance of the model. It should however be emphasised that the population of older people is highly heterogeneous and differences might be due to other (unmeasured) covariates of the panel members. For example frailty or (co)morbidity indicators might be of importance.

Differences between the characteristics of the tablets used for model development and those included in the current sample could be another reason. A comparison of the physical characteristics of the tablets included in the training and test set for model development and the tablets included in the current study is shown in Table 2. The critical parameters of the tablets included in our study are comparable to the parameters of the tablets used for model development. Also the approach taken for breaking the tablets differed between the two studies. In the previous study, participants were asked to break the tablets as they would do it themselves, i.e. without any instruction. The participants of the current study were asked to break each tablet in three different ways; with and without using nails and by pushing the tablet downward on a flat surface. Whereas the first two methods are very common and assumedly applied by the participants during the previous study, the last method is relatively

unknown and potentially not used by the previous participants. However, some tablets are developed to be broken this way. Based on the presence of tablets with a deep and wide score mark in the tablet sample used for model development, it can be assumed that the previous study also included tablets with a pressure sensitive score mark. Therefore, the outcome for breaking the tablets that contain a pressure sensitive score mark that were included in our study could be better than for tablets with a similar type of score mark included in the previous study. The model does however not underestimate the proportion of people that is able to break the tablets that contain a pressure sensitive score mark, i.e. tablet A1, B1, C1 and D1. In contrary, for tablet C1 and D1, the prediction deviated not more than 10% for the observed findings.

Oblong tablets

The criteria established for oblong tablets underestimated the actual observation for one of the two oblong tablets of our sample. The previously defined criteria for oblong tablets were based upon the minimum values for critical parameters diameter, depth of score mark, diameter/width ratio, and resistance to crushing for a set of three oblong scored tablets for which the observed ease of breaking was 100%. The researchers point out that these acceptance criteria were set conservatively. Two of the three tablets actually do not meet the criteria and would thus be considered insufficiently breakable although all participants were able to break these tablets. Our study included only two oblong tablets, B2 and D2. For tablet B2, the criteria correctly predicted that a low proportion of participants would be able to break the tablet. For tablet D2, the criteria were too restrictive as they predicted that less than 80% of the users would break the tablet whereas actually more than 80% of the participants were able to break the tablet. Using a larger sample of oblong tablets would help to optimise these criteria.

Table 2 Comparison between the physical characteristics of the tablets used for model development and the tablets included in the current study

Characteristics	Previous study		Current study
	Training set (n=20)	Test set (n=5)	(n = 9)
Resistance to crushing (*N*)	9-206	32-150	5-138
Diameter (mm)	5.9-11.0	6-13.1	5.7-10.2
Score (one or two sided)	95% one-sided	100% one-sided	80% one-sided
Thickness (mm)	1.9-4.6	2.6-4.5	2.5-3.9
Shape (flat or biconvex)	55% flat	60% flat	30% flat
Mass (mg)	90-497	100-667	90-320
Depth of score mark (mm)	0.2-0.6	0.2-1.0	-
Curvature (rad)	0.189-0.737	0.444-0.582	-
Score type (standard/pressure)	-	-	66% standard
Width of score mark	0.5-1.5	0.9-2.0	-

Recommendations to improve score mark reliability

The ease of breaking is related to physical properties of the tablet, human characteristics and the method of breaking. To ensure an acceptable ease of breaking for scored tablets in clinical practice, this multifaceted quantity would preferably be measured for each score mark using a test panel. However, this would be a time consuming and costly process. A predictive model for ease of breaking as developed previously could be a valuable tool. However, the current model requires updating. Consideration should be given to the variables of the model, as currently two of the five variables appear to be confounded, as well as to the sample size. Furthermore, the sample size should be increased by investigating the ease of breaking of an additional number tablets. Whereas the external validation previously comprised of different tablets being broken by the same test panel, it is recommended to extend this by having identical tablets being broken by different test panels. Furthermore, pressure sensitive score marks may have different critical variables compared to standard score marks. We therefore advise to develop a separate model for these tablets.

Besides updating the predictive model and optimising the criteria for oblong tablets, some best practices for scored tablets that would ensure sufficient ease of breaking could be established. Several studies indicated that it is easier to break oblong tablets compared to round tablets.[2, 3, 9, 21, 23] Tablets with a large diameter are easier to break as the force required to break a tablet becomes smaller with increased diameter and also, larger tablets are easier to hold. A deep score mark is easier to break because it decreases the thickness of a tablet. When manufacturers choose to apply a score mark on a tablet, it is recommended they rationalise the tablet geometry with respect to shape, size and depth of the score mark.

Conclusions

The model for round scored tablets and the criteria for oblong scored tablets to estimate the proportion of older people that are able to break a specific tablet are currently insufficiently reliable for use during product development. We recommend to update the predictive model for round scored tablets as well as to update the criteria for oblong scored tablets. Furthermore, we recommend that manufacturers make rational choices with regard to tablet geometry when developing tablets that bear a score mark.

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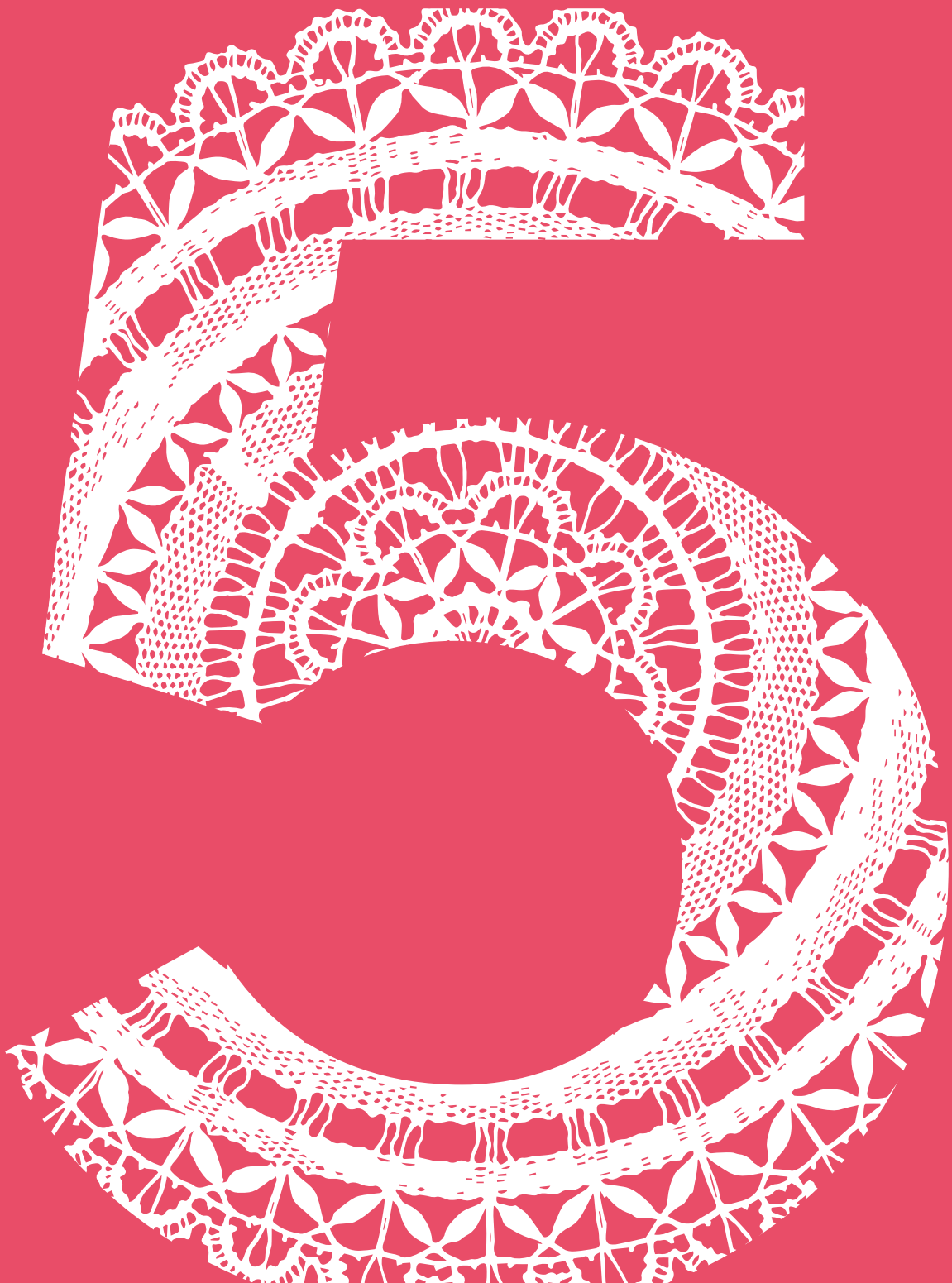
References

1. Denneboom W, Dautzenberg MG, Grol R, De Smet PA. User-related pharmaceutical care problems and factors affecting them: The importance of clinical relevance. J Clin Pharm Ther. 2005;30(3):215-23
2. Gupta P, Gupta K. Broken tablets: Does the sum of the parts equal the whole? Am J Hosp Pharm. 1988;45(7):1498
3. Helmy SA. Tablet splitting: Is it worthwhile? Analysis of drug content and weight uniformity for half tablets of 16 commonly used medications in the outpatient setting. J Manag Care Spec Pharm. 2015;21(1):76-88
4. Hill SW, Varker AS, Karlage K, Myrdal PB. Analysis of drug content and weight uniformity for half-tablets of 6 commonly split medications. J Manag Care Pharm. 2009;15(3):253-61
5. McDevitt JT, Gurst AH, Chen Y. Accuracy of tablet splitting. Pharmacotherapy. 1998;18(1):193-7
6. Notenboom K, Beers E, van Riet-Nales DA, Egberts TC, Leufkens HG, Jansen PA*, et al.* Practical problems with medication use that older people experience: A qualitative study. J Am Geriatr Soc. 2014;62(12):2339-44
7. Quinzler R, Szecsenyi J, Haefeli WE. Tablet splitting: Patients and physicians need better support. Eur J Clin Pharmacol. 2007;63(12):1203-4
8. Rodenhuis N, de Smet PA, Barends DM. Patient experiences with the performance of tablet score lines needed for dosing. Pharm World Sci. 2003;25(4):173-6
9. Spang R. [breakability of tablets and film-coated dragees]. Pharm Acta Helv. 1982;57(4):99-111
10. Tahaineh LM, Gharaibeh SF. Tablet splitting and weight uniformity of half-tablets of 4 medications in pharmacy practice. J Pharm Pract. 2012;25(4):471-6
11. Teng J, Song CK, Williams RL, Polli JE. Lack of medication dose uniformity in commonly split tablets. J Am Pharm Assoc (Wash). 2002;42(2):195-9
12. Tordoff J, Simonsen K, Thomson WM, Norris PT. "It's just routine." A qualitative study of medicine-taking amongst older people in new zealand. Pharm World Sci. 2010;32(2):154-61
13. van Santen E, Barends DM, Frijlink HW. Breaking of scored tablets: A review. Eur J Pharm Biopharm. 2002;53(2):139-45
14. Stimpel M, Kuffer B, Groth H, Vetter W. Breaking tablets in half. Lancet. 1984;1(8389):1299
15. van Vooren L, De Spiegeleer B, Thonissen T, Joye P, Van Durme J, Slegers G. Statistical analysis of tablet breakability methods. J Pharm Pharm Sci. 2002;5(2):190-8
16. Verrue C, Mehuys E, Boussery K, Remon JP, Petrovic M. Tablet-splitting: A common yet not so innocent practice. J Adv Nurs. 2011;67(1):26-32
17. Wilson MG, Kaiser FE, Morley JE. Tablet-breaking ability of older persons with type 2 diabetes mellitus. Diabetes Educ. 2001;27(4):530-40
18. Stimpel M, Vetter H, Kuffer B, Groth H, Greminger P, Vetter W. The scored tablet--a source of error in drug dosing? J Hypertens Suppl. 1985;3(1):S97-9
19. European pharmacopoeia, monograph 0478, tablets. 8th ed. Strasbourg: Council of Europe; 2013.
20. Notenboom K, Vromans H, Schipper M, Leufkens HG, Bouvy ML. Relationship between age and the ability to break scored tablets. Front Pharmacol. 2016;7:222
21. van der Steen KC, Frijlink HW, Schipper CM, Barends DM. Prediction of the ease of subdivision of scored tablets from their physical parameters. AAPS PharmSciTech. 2010;11(1):126-32
22. European pharmacopoeia, resistance to crushing of tablets; 01/2008:20908. 9th ed. Strasbourg: Council of Europe; 2017.
23. Sedrati M, Arnaud P, Fontan JE, Brion F. Splitting tablets in half. Am J Hosp Pharm. 1994;51(4):548, 50



Chapter 5

General discussion

Introduction

European health policy makers encourage older people to remain living independently in their own homes as long as possible.[1] However, the probability of chronic illness, disabilities and functional decline, e.g. with regard to decreased vision, hearing, manual dexterity and hand-grip strength, increases with age. These impairments not only limit a person's ability to carry out basic activities of daily living such as housework, cooking, bathing and dressing, but also the ability to use medication. Older people may experience problems using their medicines, for instance difficulties with the removal of medicines from their packaging, or difficulty swallowing or breaking tablets.[2-4] Failure to adhere to the prescribed medication regimen may lead to deterioration of medical conditions or to adverse effects ranging from bothersome complaints to serious reactions including disability or (re)admissions to hospital.

The ability to remain living independent in one's home frequently depends on older people's health condition and therefore, partly, of their ability to adequately manage their, often complicated, medication regimen. The practical problems that older people may experience with the use of their medicines can be reduced by taking the needs of older people into account during the development of medicinal products. Designing medication that is easy to use by older patients will not only benefit the geriatric population. Populations with overlapping usability issues and even those who are not "disabled" will benefit from more user-friendly medicines too. A thorough understanding of the problems that older people encounter using their medications will facilitate the development of user-friendly medicines.

This thesis presents a series of studies on problems that older people experience with the use of their oral prescription medicines and discusses approaches to prevent these problems. We generated an overview of the practical problems that older people encounter with the use of their medicines by conducting telephone questionnaires and face-to-face interviews with older people about their experiences with the use of their medication (Chapter 2). Next, we investigated the suitability of the design of medicines for use by older people by identifying and evaluating the design aspects of medicines that were related to practical problems with medication use in daily practice (Chapter 3). Further, we explored approaches to prevent the occurrence of usability problems. This concerned attention for problems with the use of medicines by pharmacy staff, overcoming problems with the swallowing of medicines by intake with small portions of food and the evaluation of the ease of breaking scored tablets (Chapter 4).

This final chapter summarises the main findings in this thesis, and discusses the approaches and challenges in reducing the practical problems that older people experience with the use of their medicines. These approaches and challenges are discussed for relevant stakeholders that are involved in the development, evaluation, prescription and dispensing of medicines.

Main findings in this thesis

Taking medicines as recommended involves the reading and understanding of the package insert, opening and removing the medicine from the outer and inner packaging, any preparation before use, and finally, the actual administration of the medicine. This thesis shows that older people experience a variety of practical problems with any of these tasks. The main findings are as follows.

- Patients often do not read the patient information leaflet either because they are unable to read or understand the information or because they conscientiously decide not to read information that they regard as worrisome. Worrisome information may also result in patients who take a lower dose than prescribed or not take the medicine at all. (Chapter 2.2)

- Patients often struggle with the opening of the packaging. They ask others (e.g. relatives, friends or home-care) to assist them with opening of packaging, but they may also use a jar opener, scissor or knife. Problems are particularly experienced with the opening of tamper-evident and child-resistant closures. (Chapter 2.1, 2.2, 3.2)

- Removing tablets or capsules from blister packs can be difficult, particularly when this concerns peel-off blisters. This may also result in tablets that break or crumble when removing them from a blister. (Chapter 2.1, 2.2)

- Patients have difficulty identifying their medicines when they are stored outside their commercial packaging, mostly due to similarity in appearances. (Chapter 2.2)

- Breaking tablets was reported as difficult and/or painful. A considerable proportion of patients do not succeed in breaking tablets or end up with unequal parts or crumbles. Older people encounter considerably more problems with the breaking of scored tablets compared to young adults. (Chapter 2.2, 3.1)

- Patients experience difficulties with the swallowing of medicines. This may concern lodging of the medicine in the mouth or throat, but swallowing can also be difficult as

the medicine has an unpleasant flavour or when tablets are too small for patients to keep track of them in their mouth. Swallowing problems are often overcome by taking the medicine with a small portion of food. (Chapter 2.2)

- The practical problems experienced with the use of medicines or the strategies applied to overcome these problems could adversely affect the safety or efficacy of the medicine. (Chapter 2.2)

- Although pharmacy technicians are aware of the problems that people may experience with the use of their medications, we found that there is no systematic attention for such problems during dispensing in most pharmacies. (Chapter 4.1)

- The provision of alternative administration techniques in the product administration to overcome swallowing problems with tablets and capsules can be simulated by simple *in vitro* tests to screen for potential incompatibility issues between medicines and small portions of foods. (Chapter 4.2).

- The ease of breaking scored tablets is difficult to predict based on the physical characteristics of a tablet such as size and shape. However some general criteria may be defined (Chapter 4.3)

Approaches and challenges for stakeholders

Problems with the use of medicines can result in inconvenience, poor adherence and medication errors. Whereas poor adherence and medication errors on itself receive increasingly more attention, e.g. through the conduct of medication reviews by pharmacists, practical issues with the use of medicines are often overlooked.

The intrinsic user-friendliness of medicines can much be improved, however, issues with the use of medication will always remain. Healthcare professionals can contribute more to the prevention and solving of these residual problems. All actors involved in the development, evaluation, prescription and dispensing should collaborate to ensure that medicines are used correctly. The users themselves may also contribute.

Figure 1 Stakeholders involved in proper use of medicines

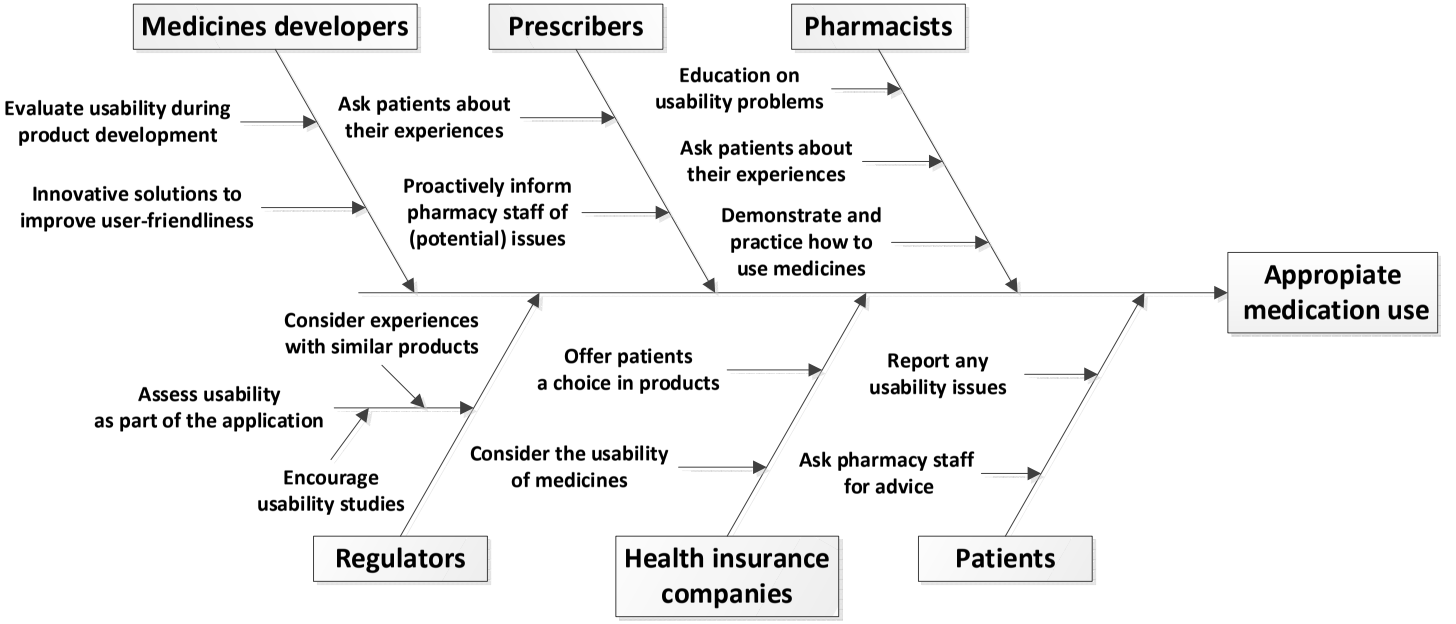
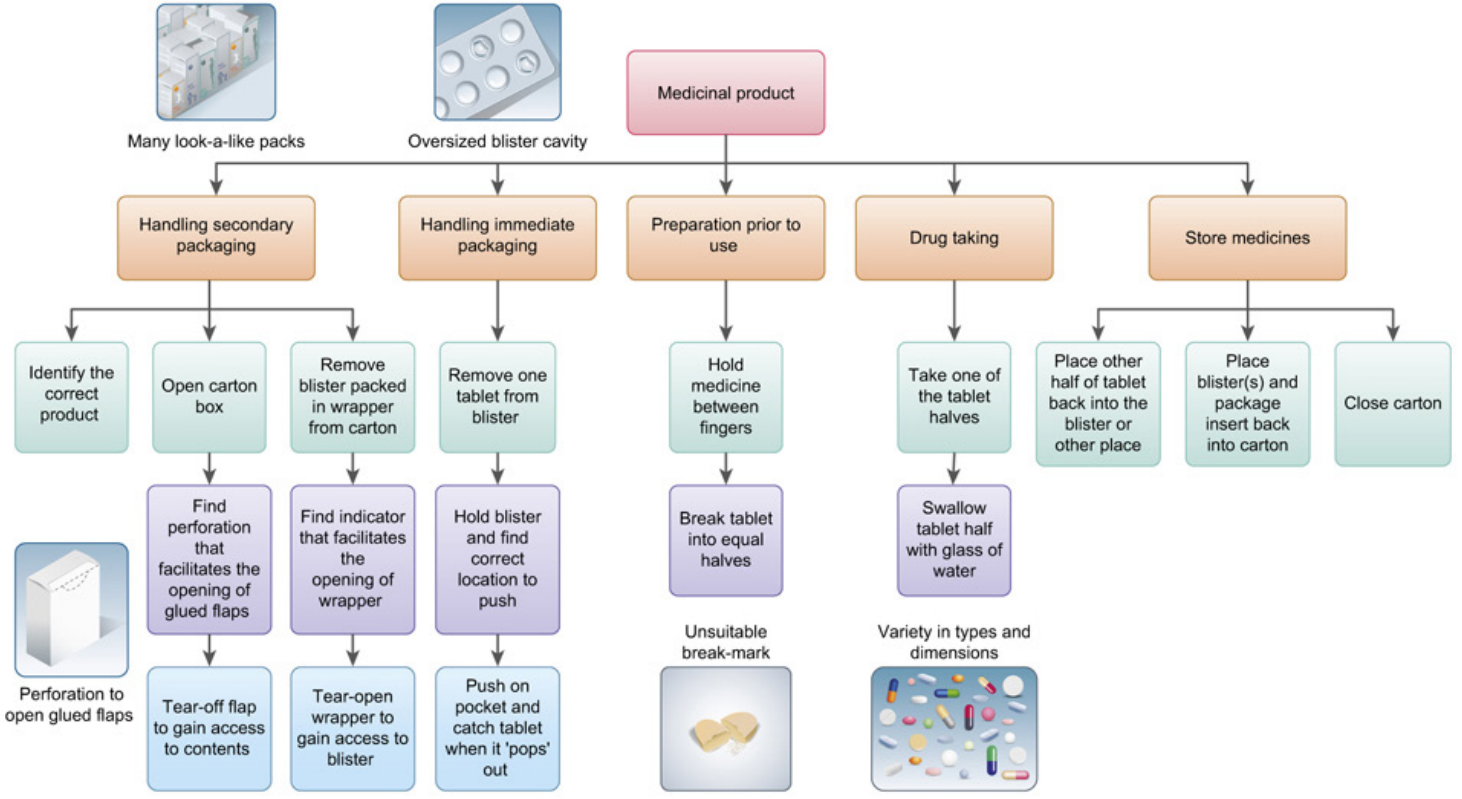


Figure 2 **Task analysis showing the individual tasks involved in taking half a tablet packed in blister packaging**



Medicines developers

The variety of use problems identified by the studies described in Chapter 2.1 and 2.2 demonstrate that medicines often lack a design that takes the needs of the older user population into account. The user-friendliness of medicines could be improved when efforts are directed to that goal. As shown by the task-analysis in Figure 2, using a tablet packed in a blister involves many tasks during which patients may encounter difficulties. Studying how patients interact with their medicines while using them, as done through human factors engineering, could benefit the independence and eventually quality of life of older people. The taxonomy of the identified problems provided in Chapter 2.2 can be used as a framework for the development of user-friendly medicines.

It is, however, not necessary to prospectively identify all potential usability problems for every individual drug by such techniques. Many usability problems are relatively easy to foretell. For example, one of the main findings in this thesis concerns the high number of reported difficulties with the opening of tamper-evident packaging, including carton boxes with glued flaps or carton boxes closed by a sealing label (Chapter 3.2). The perforation lines to open a glued carton box and the sealing labels are often poorly visible, especially for patients suffering from impaired vision. In addition, patients are often not aware of the presence of these features. The loss of manual dexterity may further reduce patients' ability to open such packaging. The use of perforation lines and sealing labels should therefore be avoided for medicinal products that are indicated for conditions that are likely to impair older patients' vision or manual dexterity, such as glaucoma, rheumatoid arthritis or Parkinson's disease. For other products, perforation marks could be accentuated by a coloured dotted line and sealing labels can be coloured or receive tangible features. Still, additional consideration should be given to the ease of opening of the perforation lines and sealing labels, especially for products intended for use in a geriatric population.

Besides impeding the ease of opening, tamper verification features hinder pharmacists in getting informed of the characteristics of the medicines they dispense to their patients as they need to break the tamper evident seal when they want to look at the product they are dispensing or if they want to read the patient information leaflet. From February 2019, all pharmaceutical packaging marketed in the European Union needs to be equipped with tamper verification features. It is a challenge for medicine developers to find a balance between tamper evidence, usability and sufficient opportunity to inform patients on drug characteristics.

Another example of a potential usability problem that is easy to foretell concerns difficulty distinguishing between different tablets. This has been reported during the qualitative study

described in Chapter 2.2 for tablets stored outside their original packaging, e.g. in multi-dose dispensing system, for tablets stored outside the outer carton but inside their blister and even for tablets stored in their original container. One participant reported difficulty distinguishing between two different strengths of Madopar® tablets (levodopa + benserazide). The higher strength was intended to be used for maintenance therapy of Parkinson's whereas the other strength was for incidental use during 'off'-symptoms. This patient unintentionally mixed up the two strengths due to the resemblance in their appearance, resulting in both under- and overdosing and consequently worsened disease control. Both tablet strengths have a similar shape and colour; the distinguishing features were a slightly smaller diameter and the presence of an embossment on one side of the higher strength tablet. Furthermore, the outer cartons and containers of both strengths have similar appearances. Bearing in mind that many patients with Parkinson's disease use more than one strength in a similar way and that one of the symptoms of Parkinson's is mild cognitive impairment, drug developers should have anticipated on this mix up by choosing greater differences in shapes and/or different colours for the two tablet strengths. In addition, the use of different colours on the packaging could contribute to avoiding a mix-up as well.

The usability problems described above are not only easy to predict; they are also relatively easy to avoid. Some usability problems are however more complex to overcome. For instance, difficulties experienced with the use of score marks. Breaking tablets is required for about 10% of the prescribed tablets.[5, 6] Following the nine reports regarding difficulty breaking tablets by the 59 older patients that we interviewed about their experiences with their medicines (Chapter 2.2), we investigated the suitability of score marks further by comparing the ability of breaking between older and young adults (Chapter 3.1). This study showed that older people experience considerably more problems with the breaking of scored tablets compared to young adults. At the same time, older people are likely to more often need to break tablets. Ideally, tablets that will be used predominantly in the geriatric population, such as medicines for the treatment of Alzheimer's disease, Parkinson's disease, urinary incontinence, and cardiovascular disease, should be available in the typical strengths that are frequently used in this population in order to prevent the need to break tablets to obtain the required dose. This is especially important for drug substances with a narrow therapeutic window. When a score mark is applied, the physical parameters of tablets should be chosen in such a way that sufficient ease of breaking is likely. The study described in Chapter 4.3 shows that it is difficult to predict the ease of breaking upon the physical characteristics of a tablet. However, sufficient evidence is available to conclude that the best features of scored tablets are an oblong shape, large diameter, a deep score mark and low hardness.[7-10]

The study presented in Chapter 3.2 showed that push-through blisters and tamper evident packaging contributed the most to the occurrence of use errors. From the telephone interview discussed in Chapter 2.1 it was found that the less commonly available peel-off blisters are found even more difficult to use than push-through blisters. The main issue with the use of these blisters is that users are often not aware that their medication is supplied in peel-off blisters. Therefore, they try to push the medicines out through the foil layer which is difficult because it is not developed for this purpose. Another reason for problem with this type of blister packaging is that the pull tab is insufficiently large enough to allow the user to grasp it to peel the layer apart. It seems that whereas great attention is given to ensure that the closure system effectively protects the product inside, little attention is given to the ease of opening. If packaging is difficult to open, patients revert to other methods to open it, such as the use of knifes or they ask others for help. Ensuring sufficient ease of opening of pharmaceutical packaging would contribute significantly to the reduction of usability problems among older adults. For medicines packed in push-through blisters, not only the push-through force of the lidding foil is a relevant factor for the ease of removing tablets and capsules, but also problems related to the size ratio between the cavities and the dosage form inside were reported. This finding is supported by a recent study that showed that a perfect fit of the dosage form in the cavity and visibility of the dosage form are key factors for the ease of removing solid dosage form from blister packs.[11, 12] For tamper-evident ring closures the force required to break and pull the ring was often found too much for older people.

Another significant challenge in container-closure design is overcoming the difficulty that older people experience with the opening of child-resistant closures. Older people often do not close these containers properly or they transfer the medicines to another, easier to handle container. This can be detrimental to the quality of the medicines, especially when the original container or the container cap contains a desiccant to protect the medicines inside from moisture degradation. This illustrates how the design of packaging brings about undesired behaviour. In the situation where a product is used within a broad user population, it might be an option to make the product available in a child-resistant as well as a senior-friendly container. Due to standardization in container-closure systems, several closures can be compatible with the same container. Medicine developers could make use of this and provide pharmacists the option to replace a closure to accommodate the needs of different user populations. This strategy may also have drawbacks. The use of non-child-resistant closures might potentially put children at risk when visiting their grandparents. So attention should also be given to developing closure systems that combines both features, i.e. it should protect children from being able to consume the medicines while giving older patients easy access.

Regulators

Whereas demonstration of the efficacy and safety of a medicinal product are a condition to marketing authorisation, demonstration of its usability is not, despite that improper use can affect the efficacy and safety of a medicine. However, the importance of product design on medication use has been recognised by regulators. Both the European Medicines Agency's (EMA) and the Food and Drug Administration (FDA) published guidance documents on how to minimize the risk of medication errors related to product design.[13, 14] In addition, the EMA is developing a reflection paper on the pharmaceutical development of medicines for use in the older population as part of the Geriatric Medicines Strategy Roadmap 2015. This reflection paper will present the current way of thinking toward geriatric product development. It shall, however, not provide guidance on how to develop medicines used in the geriatric population, i.e. it will not include explicit criteria such as a maximal acceptable size for tablets or requirements regarding the ease of opening of containers. There is also no guidance on usability testing of a dosage form and its packaging, e.g. how to select participants, what parameters to include and how to measure and express them, how to report the findings and what would be an acceptable success rate.

The lack of guidance on the usability testing of medicines limits regulators in their possibilities to request medicine developers to demonstrate or improve the usability of a proposed medicinal product prior to marketing. Changes to the design of a dosage form, packaging or measuring device are generally implemented following issues identified through post-marketing reports. A recent example thereof are the reported cases regarding difficulty swallowing of Xtandi® (enzalutamide) capsules, indicated for the treatment of progressive prostate cancer. Xtandi® is presented as a soft capsule that contains the enzalutamide in a liquid formulation. The recommended dose is 160 mg given once daily, which represents four capsules that contain 40 mg of Enzalutamide each. The capsules have a size of approximately 20 mm x 9 mm, which is the largest capsule size in use. The patient should swallow the capsules without chewing, dissolving or opening prior to swallowing. Post marketing reports demonstrated that the swallowability of this product represents serious problems for the generally severely ill, mostly bedridden, older men that are suffering from the disease and side effects of the therapy itself.[15] The choice to develop liquid containing capsules was based on early animal studies that demonstrated that bioavailability was greater when enzalutamide was dosed as a solution rather than as a suspension or solid formulation. The European Public Assessment Report for Xtandi® does not describe whether it has been considered if the higher bioavailability in solution compensates for the consequential large size of the capsules. It is merely mentions that the size of the capsules in 'reasonable'.[16] The company has initiated the development of tablets with smaller dimensions.[17] Based on

the case reports regulators may decide not to accept this large capsule size for any other product intended to be used in a similar population.

Collecting and sharing post-marketing reports on usability problems with medicines could significantly contribute to the prevention of similar problems with other products. Of course, preventing problems with the use of medicines prior to marketing has preference over initiating measures after negative experiences by patients. Furthermore, once a marketing authorisation has been granted, the balance of power between medicine developers and regulators shifts and it unfortunately occurs that some developers delay commitments to the detriment of patients. Usability testing and human factor engineering is already common practice other fields, such as the development of medical devices, drug-device combinations and consumer goods. As discussed in Chapter 3.2, requiring the demonstration of usability testing or human factor engineering throughout the design and development process and upon submission of the dossier for marketing authorisation will lead to more user-friendly medicines. Especially when the medicinal product requires specific handling, when relatively novel features are introduced or when the intended user population is more prone to experience usability problems. In the situation where medicine developers have conducted usability studies on their medicines, they may currently be reluctant to submit the results of these studies as it is unknown how regulators will assess the outcomes thereof. The lack of guidance on the usability of medicines not only withholds the identification and prevention of potential usability problems with medicines prior to marketing, it withholds also knowledge on innovations that improve the usability of medicines. It is therefore recommended that regulators encourage the submission of usability studies, e.g. by stating that, for the time being, the information will only be used for information purposes and will not lead to additional requirements.

Areas of conflict

In some instances, safety measures may be in conflict with the usability of medication packaging. An example thereof is the Falsified Medicines Directive, which aims to prevent falsified medicines entering the legal supply chain and reaching patients. One of the measures of this directive is that all pharmaceutical packaging available in Europe needs to be equipped with anti-tampering devices.[18, 19] The increased physical strength needed to open such packaging shall negatively affect the ease of opening among older patients. In addition, specific requirements to protect the safety of one user population may be detrimental to another user population. A clear example thereof are child-resistant closures. These closures protect children from unintentional poisoning as a result of the ingestion of medicines. At the same time, these closures are frequently too difficult for older people to use properly.[3, 20, 21] Enforcing the use of child-resistant closures for all medication is therefore

not recommended. The International Organization for Standardization (ISO) has published standards for child-resistant packaging and the accessibility of packaging for consumer goods.[22, 23] The standard for child-resistant packaging specify performance requirements and test methods for packaging that has been designated child-resistant, and provides a measure of the effectiveness of the package in restricting access by children and cover the accessibility of adults between the ages of 50 and 70. The standard for accessible design specifies requirements and recommendations for the accessible design for packaging with a focus on ease of opening. Similar standards for pharmaceutical packaging would contribute to the assessment of the accessibility of medication packaging.

Further, regulatory authorities are recommended to facilitate the implementation of innovative solutions aimed to improve the user-friendliness of medicines. Examples of early developments to improve medication adherence are numbering the days of a cycle and the inclusion of empty cavities to indicate medication free days. More recently, innovations like interactive packaging that can record opening times and/or monitor storage temperature have become available. In addition, blister packs with a top opening have been introduced to the market. Such innovations however sometimes have the suspicion of being a marketing tool. Accompanying the submission of such innovations with demonstration of the claimed patient benefits by appropriate studies would help developing best practices as well as differentiating between innovations that are beneficial to patients and those that are solely beneficial from a commercial perspective.[24]

The acceptability of halved or quartered tablets as a dosage form

There is much discussion about score marks in literature. Many studies have demonstrated problems with crumbling and breaking into unequal parts, as well as with the ease of breaking. In the context of such a discussion, it is relevant to realize that the quality of a dosage given by half a tablet is already significantly less than that of a dosage given by a whole tablet. Half tablets are allowed to have about 15% variation in mass, and therewith in the delivered dose, in addition to the more stringent requirements of the pharmacopoeial technical procedures 2.9.40, 2.9.5 and 2.9.6 that are applicable to whole tablets.[25-28] For example, the mass of a 90 mg tablet containing 2.5 mg of substance X is allowed to vary by 7.5 %. Consequently, the content of active substance is allowed to variate between 2.3-2.7 mg. When a 180 mg tablet containing 5 mg of substance X is divided in half to obtain a 2.5 mg dose, the active substance is allowed to variate between 2.0-3.1 mg. On top of this, any loss of mass following breaking is not taken into account as the allowed weight variation for tablet halves of 15% is calculated from the average weight of halved tablets. Studies report a loss of mass below 1% up to 2.6%.[7, 29-31] Furthermore, compliance with the variability in mass of half tablets only needs to be demonstrated once, as part of product development, i.e. the test is performed as part of batch release testing. Besides the generous

requirements for weight variation of half tablets compared to whole tablets, whole tablets are evaluated for bioequivalence and/or similarity in dissolution behaviour with a reference product whereas such studies are not conducted for tablet halves. Moreover, no attention is given to (non-) linearity of the kinetics of the active substance when score marks are applied whereas in certain circumstances a bioequivalence study would be required on the lower tablet strength when it would have concerned a whole tablet[32]. The above discussion shows that the applied quality standards for halved tablets are much lower compared to the standards for whole tablets, and that manufactures can avoid performing dissolution and/or bioequivalence studies by applying a score mark instead of manufacturing a whole tablet. Even when manufactures demonstrate compliance with the regulatory requirements for weight variation for halved tablets, it is reported that these requirements are not met when breaking tablets in daily practice. Furthermore, problems with the ease of breaking are observed, which is not part of the evaluation of the performance of score marks.[7-9, 29, 33-37] The study described in Chapter 3.1 shows, on average, only 70% of the tablets that were broken complied with the requirements for weight variation and that older people frequently experience problems with the ease of breaking. These issues raise concerns on the reliability of score marks and consequentially, of fractional dosing. Besides fluctuations in the administered dose, bad score mark performance may have negative consequences on patient compliance with drug regimens, as patients may skip or double doses rather than breaking tablets. Regulators are recommended to reconsider the use of score marks as well the current requirements for assessment of score mark performance.

Limitations of the available product information

The patient information leaflet intends to provide patients relevant information on their medication in order to ensure that it is taken correctly and used as intended. Despite the implementation of several changes to the contents of the patient information leaflet, many patients find them poorly designed, too long, complex, font size too small, difficult to read and the folding to fit it in the package complicated.[2, 38, 39] As a consequence, many people occasionally read the leaflet or not at all.[40, 41] These findings are consistent with the findings of the qualitative study discussed in Chapter 2.2 of this thesis. As a consequence, patients might miss relevant information on how to use their medicines. Furthermore, relevant information on the use of medicines is not always present in the patient information leaflet. During the study on the performance of score marks described in Chapter 3.1, it was noticed that only one of the four tablets that contained a pressure sensitive score mark included an instruction on how to break this tablets. Patient information leaflets lack balance between information on benefits versus harm. The correct use of medicines could be improved by making the information on the benefits of the medicine more prominent. As from 2011, EU regulatory bodies already allowed that information on the benefits of using the medicine

can be included in the patient information leaflet 'as long as it is compatible with the SmPC, useful for the patient and not of a promotional nature. However, the majority of leaflets still do not contain clear or adequate information about the potential benefits of medicines.[42] Also, including additional information increases the length of the leaflet. The provision of information to patients could also be optimised by presenting relevant instructions on the use of the medicine separately from the lengthy patient information leaflet. For instance, when packaging medicines in an outer carton with a top opening, the inside of the opening flap can be used to provide brief information on how to administer the medicine. Another option would be to provide a separate brief instruction leaflet related to the administration of the medicines. This approach is already common for consumer goods, e.g. many electronical devices come with a quick start guide. Providing information digitally to patients could also be beneficial, however the current population of elderly is not ready for this.[41]

Another drawback of the patient information leaflet is the lack of information on the stability of the medicines at the patient's home. All medicinal products need to be protected through distribution and storage until the moment of use by the patient. The packaging will protect the product from environmental influences that can alter the medicine, such as moisture and light. Medicine developers conduct stability studies on their medicine and its packaging and based on the stability data they provide a storage recommendation that assures the safety and efficacy of the medicinal product for the shelf life indicated on the package. For medicines available in multi-dose packaging, such as containers or bottles, this may also concern an in-use shelf-life. The storage recommendations do however not cover storage of medicines outside their original packaging. At the most it is mentioned that the product should be stored in its original packaging to protect from light and/or moisture. However, medicines are often stored outside their original packaging. In the Netherlands, most medication is dispensed for a period of three months. Because of the often quite bulky packaging, people frequently remove blisters from their secondary packaging and store them, for instance, in a dedicated household box. Some people additionally remove medicines from their primary packaging to store them in a small, easy to carry box for daily use. People also transfer their medicines to containers they find more easy to use. Furthermore, as a result of the increased number of drugs often to be taken a day, older people also regularly store their medicines outside their original packaging in multi dose dispensing systems. Medication may even be dispensed by the pharmacy in such dosing administration aids. However, storage of the medicinal product outside the original packaging exposes medicines to environmental factors from which their original packaging protected them. This may cause degradation of the active substance and the formation of toxic degradation products, resulting in loss of treatment efficacy or safety issues. The Dutch healthcare Inspectorate recently published a warning to inform pharmacist and patients

not to remove Pradaxa® (dabigatran etexilate) capsules from their original packaging as dabigatran is very sensitive for moisture degradation.[30, 31, 43] Other potential consequences of exposure to environmental factors are changes in the appearance, changes in the hardness of tablets, capsules becoming brittle, or changes in disintegration and dissolution behaviour. For instance, patients reported that methylphenidate retard tablets burst open when stored outside their original container[44]. During one of the interviews we conducted, a participant reported that she discovered that the appearance of her carbasalate calcium effervescent tablets changed after she transferred them for storage to a teacup. Also, the tablets no longer dissolved properly. She now stores these tablets in an empty, closed, Pantozol® container, as she is not able to open the original carbasalate container by herself.

The storage of medicinal products outside their original packaging, may not be recommended, but is unfortunately not avoidable. For people to participate in daily live, medicines needs to be transported, for instance on day trips, when visiting family or even when doing groceries. When using multiple medicines, it is almost irrational to expect them to carry all their medicines in their original packaging. Furthermore, pill organizers or systems people develop themselves at home support people in complying with their often complicated medication regimens. It is therefore recommended that information on the storage of medicinal products outside their original packaging becomes available. The current recommendation that medicines should be stored in their original packaging to protect them from light and/or moisture could be extended with information on the period within these environmental effects become detrimental to product quality. This would allow pharmacists and patients to make informed choices on the dispense and storage of medicines in multi-dose dispensing system by pharmacists. For product that must be stored under refrigerated conditions, the provision of information on the effects of occasional storage outside these conditions is relevant.[45]

Healthcare professionals

Effective collaboration between general practitioners, specialists and pharmacists plays an important role in preventing and overcoming usability problems with medicines both in hospitals and in primary care. Physicians generally have knowledge on a patient's clinical status and physical capabilities and are therefore in the position to foresee certain difficulties with the use of the medicines they prescribe to a specific patient. Patients may also report usability problems to their physician. When such information is proactively shared with the pharmacy, the suspected usability problems can be addressed during counselling. For example, when a pharmacist knows that a patient suffers from dysphagia, the pharmacist can discuss potential problems with the swallowing of medicines, provide

swallowing instructions and look for the most suitable formulation for this patient, e.g. liquid or dispersible formulations. Prescribers can however not foresee all usability problems, as they generally do not know all details of the medicines they prescribe. For instance, they may not be aware of the size of a capsule or tablet, or the presence of a container with a child-resistant closure. Consequently, pharmacists also play a key role in the prevention of usability problems through counselling. The case regarding the difficulty distinguishing the two look-a-like Madopar® tablet strengths was identified at the pharmacy and resolved by writing "OFF" on the pharmacy label attached to the container of the lower strength tablets. As discussed in Chapter 4.1, we recommend that asking about patients' experiences with the use of their medicines becomes an integrated part of counselling by pharmacists. In addition, a patients' ability to perform specific tasks to use his medication such as breaking a tablet should be assessed and practiced at the pharmacy.

The study described in Chapter 4.1 revealed that usability problems are not systematically addressed during medication dispensation, i.e. technicians usually only discuss the problems when patients bring them up themselves. We also found that some technicians feel insecure with respect to counselling on these practical issues. It would be of added value to provide education on addressing usability problems. Especially because not all solutions are suitable for all medicines, e.g. not all medicines can be transferred to another container without affecting their stability. For instance, tablets that are packed in a container that includes a desiccant for moisture absorption or products for which the labelling clearly state that it should be stored in the original packaging to protect the medication from light and/or moisture. It is important that pharmacy technicians are aware of the implications of non-compliance with the storage recommendations and other relevant user information so that they can inform patients thereof and find suitable solutions to overcomes there usability problems.

The study described in Chapter 2.1 demonstrated that patients experience more problems with the removing of medicines from peel-off blisters compared to medicines packaged in push-through blisters or containers. With the study on the breakability of tablets described in Chapter 3.1 we noticed that none of the 72 participants was aware of the existence of pressure sensitive tablets and how to break them. Both these findings may be explained by the fact that peel-off blisters and pressure-sensitive tablets are relatively uncommon features. Because learning new skills becomes more difficult with age (refs), specific attention should be given to the use of medicines that are dispensed with relatively uncommon design aspects. However, pharmacy staff does not always have knowledge of the design features of medicines because these are not visible from the outer packaging. Informing pharmacy staff about the design features of medicinal products would facilitate

foreseeing potential usability problems and to provide relevant instructions on the use of the medicine. The possibility to check these aspects of medicines are also impeded by tamper-evident packaging.

Most patients but also pharmacy staff is not always aware of the impact of non-compliance with the storage recommendations. Patients may also not understand the purpose of a desiccant. One person we interviewed used perindopril tablets, which are supplied in blisters that are each packed in an aluminium pouch that contains a desiccant capsule. He mentioned to use the desiccant to push the tablets out of the blister, as the cups are actually too close to each other to push the tablets out with his fingers. He found it very thoughtful of the manufacturer to provide a tool for this. Other interviewees mentioned to transfer their medicines to another container they found more easy to use, although the original container contains a desiccant inside its cap.

Health insurance companies

The main objectives of medicines policy are access, quality and rational use of medicines. One of the components to ensure access to medicines it the affordability of medicines. To encourage price competition between generic manufacturers, health insurance companies in the Netherlands but also in many other countries, are allowed to assign 'preferred suppliers' for many generic drugs. Only the products of the preferred supplier will be reimbursed, whereas patients have to pay out of their own pocket for alternatives. Partly due to this preference policy the prices of generic medicines reduced significantly, which contributed to a notable decline in expenditure on medicines.

However, the preference policy also has some drawbacks. One of these drawbacks concerns the lack of patient choice between the brands of medicines. As a result of the price competition, health insurers regularly switch between preferred suppliers of a certain medicine. Subsequently, patients receive medicines from different suppliers and are therefore frequently exposed to changes in, for instance, the appearance of their medicines, the way the packaging needs to be opened or how to break the tablet. Especially for older people that use multiple medicines, this leads to confusion and inconvenience. Also, if they are used to or prefer a specific brand of a certain medicine, patients cannot keep using it when it is no longer the preferred supplier. Contrary to non-prescription medicines, for which patients can choose to buy, for example, large flat round uncoated paracetamol tablets or more expensive smaller biconvex oblong film-coated paracetamol tablets that are easier to swallow.

It is recommended that patients are offered a choice between suppliers of prescription medicines so they can choose to use a product that fits their personal needs or preferences. This would fit into one of the steps of the Dutch medicines plan, "appropriate medication use" which aims to ensure that patients do better at keeping to their treatment and at using their medications according to the prescription.[46] Health insurers are recommended to take the usability of a medicine into account when selecting preferred suppliers and be willing to pay a little bit extra when the benefits of a certain product are evident for an individual patient. In addition, co-payments could be installed if the product that the patient prefers exceeds a reference price. This will help to contain drug costs, but still gives patients some more freedom of choice. More focus on user needs will lead higher levels of patient satisfaction, which in its turn is beneficial to medication adherence. Health care insurance companies should therefore stand up for their patients and demand the availability of user-friendly medicines.

Patients

The studies in this thesis demonstrate that older people experience many problems with the use of their medicines. At the same time, the study on pharmacy technicians' attention to problems with medication use (Chapter 4.1) revealed that patients rarely spontaneously report usability problems in the pharmacy. Also other studies show that people are not forthcoming about problems with the use of their medicines.[47, 48] During the interviews of the study described in Chapter 2.2, several people mentioned that they did not want to nag about these problems at the pharmacy. However, community pharmacy staff can offer appropriate solutions to solve usability problems. One of the interviewed patients mentioned that after she informed her pharmacist she was not able to open a specific medicine container, she received those medicines in one of the pharmacies own containers which she was able to open easily. The solutions that patients come up with themselves to overcome experienced problems demonstrate creativity and resourcefulness, however, patients are not aware when their solutions are suboptimal and lead to incorrect medication use with potentially clinically relevant consequences. For instance, a participant reported to overcome difficulties with swallowing ferrous fumarate tablets by taking them with yogurt. Yoghurt contains calcium which will decrease the absorption of iron tablets.

Identifying, preventing and overcoming problems with the usability of medicines is a specific aspect in the area of pharmaceutical care that is best resolved at the pharmacy level. Health care providers should encourage patients to report their usability problems.

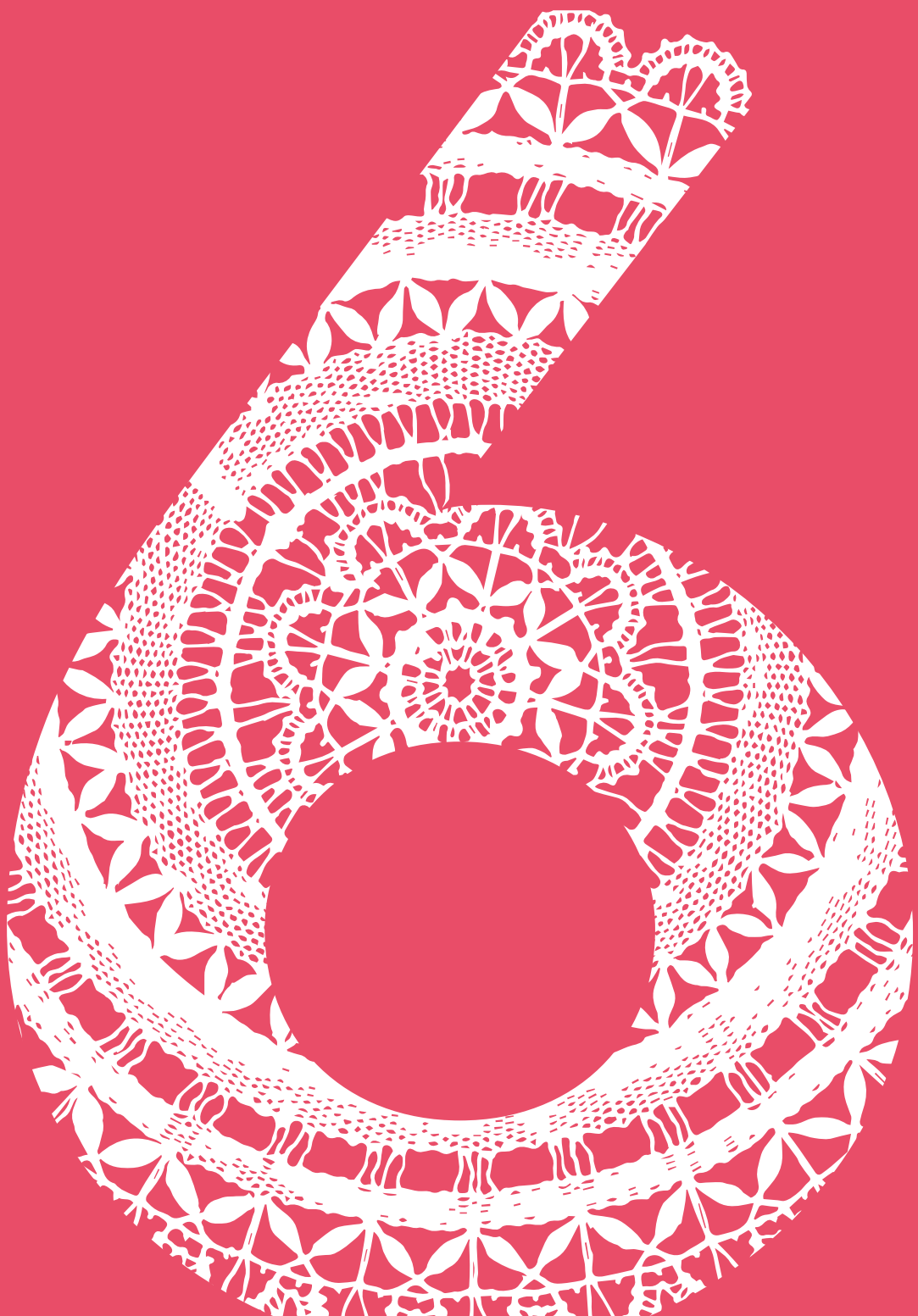
Concluding remarks

The aging of the population comes with the multifaceted challenge of how to enable older people to participate in a world that continues to develop without keeping their capabilities in mind. The findings presented in this thesis illuminate the problems of older people living at home with the use of their medicines and reveal the complexity of ageing and the use of medicines, which often requires a need for assistance or the use of kitchen tools. Older people encounter difficulties with many more aspects of their daily life besides the use of their medicines. However, where other markets have started developing products specifically for older people, such as smartphones, card holders and playing cards with large print and gardening tools, the development of medicines has stayed behind. Through the development of more user-friendly medicines, the self-use of medicines can be improved, leading to better compliance with a medication regimen and making daily life easier. Preventing usability problems with medicines is of paramount importance, since the ability to self-manage one's medication regimen will keep a person independent and in the best possible health condition. However, this requires a multifaceted approach; not only medicine developers can contribute to the better use of medicines, also regulatory agencies, health care providers, health insurers and patients themselves should be committed to contribute to this.

References

1. European commission. The 2012 ageing report: Economic and budgetary projections for the 27 eu member states (2010-2060). Brussels: European Economy; 2012.
2. Kairuz T, Bye L, Birdsall R, Deng T, Man L, Ross A*, et al.* Identifying compliance issues with prescription medicines among older people: A pilot study. Drugs Aging. 2008;25(2):153-62
3. Atkin PA, Finnegan TP, Ogle SJ, Shenfield GM. Functional ability of patients to manage medication packaging: A survey of geriatric inpatients. Age Ageing. 1994;23(2):113-6
4. Tordoff J, Simonsen K, Thomson WM, Norris PT. "It's just routine." A qualitative study of medicine-taking amongst older people in new zealand. Pharm World Sci. 2010;32(2):154-61
5. Quinzler R, Schmitt SP, Pritsch M, Kaltschmidt J, Haefeli WE. Substantial reduction of inappropriate tablet splitting with computerised decision support: A prospective intervention study assessing potential benefit and harm. BMC Med Inform Decis Mak. 2009;9:30
6. Berg C, Ekedahl A. Dosages involving splitting tablets: Common but unnecessary?
7. Gupta P, Gupta K. Broken tablets: Does the sum of the parts equal the whole? Am J Hosp Pharm. 1988;45(7):1498
8. Helmy SA. Tablet splitting: Is it worthwhile? Analysis of drug content and weight uniformity for half tablets of 16 commonly used medications in the outpatient setting. J Manag Care Spec Pharm. 2015;21(1):76-88
9. Spang R. [breakability of tablets and film-coated dragees]. Pharm Acta Helv. 1982;57(4):99-111
10. van der Steen KC, Frijlink HW, Schipper CM, Barends DM. Prediction of the ease of subdivision of scored tablets from their physical parameters. AAPS PharmSciTech. 2010;11(1):126-32
11. Braun-Munker M, Ecker F. Ease of opening of blistered solid dosage forms in a senior citizens target group. Int J Pharm. 2015
12. Muhlfeld L, Langguth P, Hausler H, Hagels H. Influence of blister package design on usability among older adults. Int J Clin Pharm. 2012;34(4):553-60
13. Good practice guide on risk minimisation and prevention of medication errors, EMA/606103/2014. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) (2015).
14. Safety considerations for product design to minimize medication errors, Food and Drug Administration. Center for Drug Evaluation and Research (CDER) (2016).
15. Enzalutamide and difficulty swallowing the capsules. Bijwerkingencentrum Lareb, 2016.
16. Xtandi: Epar - public assessment report. London: European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP).
17. Openbaar verslag 868e vergadering van het college ter beoordeling van geneesmiddelen. Utrecht: 24 November 2016.
18. Directive 2011/62/eu of the european parliament and the council of 8 june 2011 amending directive 2001/83/ec on the community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products, European Commission (2011).
19. Commission delegated regulation (eu) 2016/161 of 2 october 2015 supplementing directive 2001/83/ec of the european parliament and of the council by laying down detailed rules for the safety features appearing on the packaging of medicinal products for human use, European Commission (2015).
20. Keram S, Williams ME. Quantifying the ease or difficulty older persons experience in opening medication containers. J Am Geriatr Soc. 1988;36(3):198-201
21. Bix L, de la Fuente J, Pimple KD, Kou E. Is the test of senior friendly/child resistant packaging ethical? Health Expect. 2009;12(4):430-7
22. International organization for standardization. Child-resistant packaging - Requirements and testing procedures for reclosable packages. ISO 8317:2015
23. International organization for standardization. Packaging - Accessible design - Ease of opening. ISO 17480:2015
24. Musaus JW, Bahr M. The increasing trend of adherence packaging and the implications to manufacturing. Pharmaceutical Engineering. 2012;32(5):1-7

25. European pharmacopoeia, monograph 0478, tablets. 8th ed. Strasbourg: Council of Europe; 2013.
26. European pharmacopoeia, uniformity of dosage units; 04/2017:20940. 9th ed. Strasbourg: Council of Europe; 2017.
27. European pharmacopoeia, uniformity of mass of single-dose preparations; 01/2008:20905. 9th ed. Strasbourg: Council of Europe; 2017.
28. European pharmacopoeia, uniformity of content of single-dose preparations; 01/2017:20906. 9th ed. Strasbourg: Council of Europe; 2017.
29. McDevitt JT, Gurst AH, Chen Y. Accuracy of tablet splitting. Pharmacotherapy. 1998;18(1):193-7
30. Stimpel M, Kuffer B, Groth H, Vetter W. Breaking tablets in half. Lancet. 1984;1(8389):1299
31. Stimpel M, Vetter H, Kuffer B, Groth H, Greminger P, Vetter W. The scored tablet--a source of error in drug dosing? J Hypertens Suppl. 1985;3(1):S97-9
32. Guideline on the investigation of bioequivalence, CPMP/EWP/QWP/1401/98 Rev. 1/ Corr. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) (2010).
33. Rodenhuis N, de Smet PA, Barends DM. Patient experiences with the performance of tablet score lines needed for dosing. Pharm World Sci. 2003;25(4):173-6
34. Quinzler R, Szecsenyi J, Haefeli WE. Tablet splitting: Patients and physicians need better support. Eur J Clin Pharmacol. 2007;63(12):1203-4
35. Denneboom W, Dautzenberg MG, Grol R, De Smet PA. User-related pharmaceutical care problems and factors affecting them: The importance of clinical relevance. J Clin Pharm Ther. 2005;30(3):215-23
36. Wilson MG, Kaiser FE, Morley JE. Tablet-breaking ability of older persons with type 2 diabetes mellitus. Diabetes Educ. 2001;27(4):530-40
37. Verrue C, Mehuys E, Boussery K, Remon JP, Petrovic M. Tablet-splitting: A common yet not so innocent practice. J Adv Nurs. 2011;67(1):26-32
38. Dickinson R, Hamrosi K, Knapp P, Aslani P, Sowter J, Krass I*, et al.* Suits you? A qualitative study exploring preferences regarding the tailoring of consumer medicines information. Int J Pharm Pract. 2013;21(4):207-15
39. Raynor DK, Blenkinsopp A, Knapp P, Grime J, Nicolson DJ, Pollock K*, et al.* A systematic review of quantitative and qualitative research on the role and effectiveness of written information available to patients about individual medicines. Health Technol Assess. 2007;11(5):iii, 1-160
40. Kimberlin CL, Winterstein AG. Expert and consumer evaluation of consumer medication information-2008. https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ReportsBudgets/UCM163783.pdf2008.
41. Hammar T, Nilsson AL, Hovstadius B. Patients' views on electronic patient information leaflets. Pharm Pract (Granada). 2016;14(2):702
42. Dickinson R, Raynor DK, Knapp P, MacDonald J. How much information about the benefits of medicines is included in patient leaflets in the european union? - a survey. Int J Pharm Pract. 2017;25(2):147-58
43. Robertson SG, Glass BD. Stability of repackaged dabigatran etexilate capsules in dose administration aids. European Journal of Hospital Pharmacy. 2017
44. Meldpunt medicijnen: Instituut voor Verantwoord Medicijngebruik; Cited 18 May 2017.
45. Vlieland ND, Gardarsdottir H, Bouvy ML, Egberts TC, van den Bemt BJ. The majority of patients do not store their biologic disease-modifying antirheumatic drugs within the recommended temperature range. Rheumatology (Oxford). 2016;55(4):704-9
46. Summary of medicines plan 2016: Ministry of Health, Welfare and Sport; Cited 18 May 2017.
47. Lau ETL, Steadman KJ, Mak M, Cichero JAY, Nissen LM. Prevalence of swallowing difficulties and medication modification in customers of community pharmacists. Journal of Pharmacy Practice and Research. 2015;45(1):18-23
48. Schiele JT, Quinzler R, Klimm HD, Pruszydlo MG, Haefeli WE. Difficulties swallowing solid oral dosage forms in a general practice population: Prevalence, causes, and relationship to dosage forms. Eur J Clin Pharmacol. 2013;69(4):937-48



Chapter 6

Summary and Samenvatting

6.1

Chapter 6.1

Summary

This thesis addresses the user-friendliness of medicines. Using medicines is a complex process during which many difficulties can be experienced, for instance with the opening of packaging, the breakability of tablets or the administration of eye drops. Such practical problems can cause or lead to incorrect use of medicines and consequently into deterioration of medical conditions or to adverse effects ranging from bothersome complaints to serious reactions including disability or (re)admissions to hospital.

The correct use of a medicine depends not only of the complexity of its use but also of the capability of the user to carry out the required tasks. We took the usability of medicines for older people as a starting point for our studies. Aging comes with an increased prevalence of disabilities and functional decline, e.g. with regard to decreased vision, hearing, manual dexterity and hand-grip strength. Consequently, aging can affect a patient's ability to use medicines as required. Besides, older people are the largest user group of medicines. Taking the capabilities of the aging population into account during the development of medicines will help older people to use their medicines independently. Designing medication that is easy to use by older patients will also benefit populations with overlapping usability issues and even those who are not "disabled" will benefit from more user-friendly medicines too.

This thesis consists of three sections. Chapter 2 focuses on the practical problems that older people experience with the daily use of their medication. The studies reported in Chapter 3 address the suitability of the design of medicines for use by older people. Chapter 4 focusses on the prevention of usability problems with medicines. Finally, the results of these studies are summarised and put into a broader perspective in Chapter 5 with the aim to provide recommendations to improve the user-friendliness of medicines.

The experiences of older people with medication use

Chapter 2 starts with a description of the results of a telephone questionnaire among 317 patients aged 65 years or above about their experiences with the packaging of omeprazole tablets and capsules. Omeprazole tablets and capsules are supplied to the Dutch market in bottles, push-through blisters and peel-off blisters. The study revealed that about one in four patients experienced one or more problems with the opening of their omeprazole packaging. Most problems were experienced with peel-off blisters; two-thirds of the respondents using this packaging experienced problems therewith. Patients who received omeprazole in a bottle reported the fewest problems with opening the package. Two-thirds of patients reported management strategies for their problems. This includes help from partners, family and neighbours, the use of household tools and transferring the medicines

to another container. These findings demonstrate that the usability of medication packaging can be much approved.

Chapter 2.2 continues with the investigation on the usability of both packaging and dosage form. This chapter describes the results of a qualitative study about the daily use of oral medicines by older people. Information on the practical problems that older people experience with the daily use of their medicines and the management strategies to overcome these problems was collected through semi-structured interviews with 59 community-dwelling people aged 70 and older. The participants were recruited from a community pharmacy and on a geriatric outpatient ward in Utrecht, the Netherlands, and used at least three different oral prescription medicines daily and managed their medication independently. The interviews took place at their home and all medicines used were present during the interviews. On average, participants used 6.9 prescribed oral medicines. A total of 211 practical problems and 184 management strategies were identified. The majority (95%) of the participants experienced one or more practical problem with the use of their medicines, ranging from problems with reading and understanding the instructions for use, handling the outer packaging, handling the immediate packaging, completing any preparation prior to use, and taking the medicine. An expert panel independently classified the potential clinical relevance of every identified practical problem and associated management strategy. For 10 participants (17%), at least one of their problems was considered to have the potential to cause clinical deterioration, adding up to a total of 11 potentially clinically relevant situations. Ninety-five percent of the problems were considered not to be clinically meaningful, but even so they caused inconvenience. This study demonstrates the variety of problems that older people may experience with the use of their medicines, and the potential clinical consequences thereof. The findings pose a challenge for healthcare professionals, drug developers, and regulators to diminish these problems.

The suitability of the design of medicines for use by older people

In Chapter 3.1 we compared the ability of older people to break scored tablets with that of young adults. Health characteristics such as the presence of peripheral neuropathy, decreased grip strength and manual dexterity, can affect a patient's ability to break tablets. As these impairments are associated with ageing and age related diseases such as Parkinson's disease and arthritis, difficulties with breaking tablets could be more prevalent among older adults. We observed 36 older adults and 36 young adults with breaking 12

different, scored tablets. Each tablet was broken by three common techniques for breaking tablets by hand; in between the fingers with the use of nails, in between the fingers without the use of nails and pushing the tablet downward with one finger on a solid surface. The primary outcome measures were the ability of the participants to break the tablets and the ability of the participants to break the tablets in equal halves, i.e., the accuracy of breaking. We found that the older adults experienced more difficulties to break tablets compared to the young adults. On average, the older persons broke 38.1% of the tablets, of which 71.0% was broken accurately. The young adults broke 78.2% of the tablets, of which 77.4% was broken accurately. Further analysis by mixed effects logistic regression revealed that age was associated with the ability to break tablets (OR = 50.56, $P < 0.001$), but not with the accuracy of breaking (OR = 1.19, $P = 0.364$). Problems with the ease of tablet breaking are not just a convenience issue. The occurrence of these problems will add to the complexity of the medication regimen, increasing the risk for non-adherence, medication errors and adverse drug reactions. The high prevalence of difficulties with breaking scored tablets observed in this study, stresses the need to diminish the occurrence of this problem. Healthcare providers should be aware that tablet breaking is not appropriate for all patients and for all drugs. We concluded that, to ensure safe self-management of medicines, breaking tablets should be avoided in older patients and the use of alternatives should be considered.

Chapter 3.2 investigated the design features of oral medicines that cause use problems among older patients in daily practice. During the qualitative study described in Chapter 2.2 we also collected information on the medicines' design features that were related to the use problems, e.g. the type of dosage form, the colour, shape, size, palatability, presence of coating and break mark on a medicine, and the type and characteristics of the container closure system. We differentiated between situations were a participant experienced difficulty using the medicine but did not need help nor a coping strategy, i.e. use difficulties, and situations were a patient either needed help or applied a strategy overcome the use problem, i.e. a use error. The design features were evaluated for their contribution to the occurrence of medication use difficulties and errors. A total of 158 use problems were identified, of which 45 were categorised as use difficulties and 113 as use errors. Design features that contributed the most to the occurrence of use difficulties were the dimensions and surface texture of the dosage form (29.6% and 18.5%, respectively). Design features that contributed the most to the occurrence of use errors were the push-through force of blisters (22.1%) and tamper evident packaging (12.1%). We concluded that a more patient-centred design of medicinal products will help patients to use their medicines safely and easily. We recommend to, as for medical devices, identify areas for design improvement through human factor and/or usability engineering.

Approaches to prevent usability problems with medicines

The study described in Chapter 4.1 explored to what extent pharmacy technicians identify problems with opening medicine packaging and how they assist patients in resolving these problems. We conducted a cross-sectional study that comprised semi structured interviews, with 31 pharmacy technicians in 31 pharmacies, to assess the occurrence and type of difficulties with packaging and to suggest solutions. This revealed that all pharmacy technicians recognized the occurrence of packaging problems, though patients rarely report them at the pharmacy counter. Not all pharmacy technicians are familiar with opening all packaging forms, but they all describe ways to find out how to open them, which usually only happens after patients bring up problems. Solutions suggested by the pharmacy technicians include informing and counselling, changing or manipulating the packaging, and providing assisting tools. It was concluded that although pharmacy technicians are aware that medication packaging can cause problems and are able to suggest solutions to all these problems, there is no systematic attention for packaging at drug dispensation in most pharmacies. We recommend that asking patients whether they experience problems with medication packaging should be a standard part of medication counselling. Pharmacists should encourage and support pharmacy technicians to perform such counselling.

Chapter 4.2 focuses on the development of in vitro studies for the investigation of safe co-administration of solid oral medicines with a small portion of food to overcome swallowing problems. Up to one third of the general population finds it difficult to swallow tablets or capsules, and these problems are more prevalent among older people. The swallowing of tablets and capsules can be facilitated by taking them together with a spoonful of semi-solid food or a specific swallowing-gel. Additional administration instructions are however seldom available in the product label. In order to include such a recommendation in the product label, pharmaceutical companies should verify the impact of the co-administration on the safety and efficacy of the medicine. Regulators have pointed out that this may be done through in vitro studies, but there are no recognised in vitro methods for this purpose. To facilitate the inclusion of alternative administration techniques within the product label, we investigated the suitability of in vitro disintegration and dissolution methods as screening tools for the evaluation of potential incompatibility issues between solid oral dosage forms and small portions of food. The effects of 5 ml of applesauce, vanilla custard, yoghurt and an oral gel on the disintegration of carbamazepine tablets, dabigatran etexilate capsules, lithium carbonate immediate and prolonged release tablets and two different paracetamol tablets were investigated, as well as the effects of these vehicles on the dissolution of carbamazepine

tablets. The findings show that co-administration of paracetamol, carbamazepine and lithium carbonate immediate release formulations with spoonful quantities of applesauce, vanilla custard, yoghurt and a gel lead to statistically significant and drug-dependent delays of tablet disintegration. In addition, it is shown that the co-administration of carbamazepine tablets with spoonful quantities of vanilla custard, yoghurt and gel lead to a statistically significant delay in dissolution. This study suggests that in vitro testing is likely to predict whether further investigations, e.g. biostudies, are warranted. However, more dissolution data, with drug products exhibiting different disintegration and drug release properties, would be necessary. We encourage clinical investigators to contribute to the development of in vitro screening tools by conducting in vitro studies parallel to in vivo studies.

In chapter 4.3 we investigated the performance of a previously developed model that predicts the ease of breaking of oblong and round scored tablet based on their physical characteristics. This statistical model was developed using outcomes for actual ease of breaking obtained by a test panel and predicts the proportion of people able to break a specific tablet. The model can be a valuable tool for evaluating score mark performance during the development of scored tablets. We investigated the predictive performance of the model for oblong and round tablets by comparing the predicted breaking ease with actual outcomes in a test panel (n=36). The outcomes for round tablets show that the observed and predicted findings do not correspond well. The unsatisfactory predictive ability may be explained by the small sample size used for model development, but also by differences between the participants, setting and tablets involved in the development of the model and the current study. For oblong tablets, the model underestimated the actual observation. This finding is in line with the remark of the researchers that developed the model that the criteria for oblong tablets were set conservatively. We concluded that the model for round tablets is currently insufficiently reliable for use during product development. However, choosing oblong tablets with a diameter of ≥ 10 mm, a diameter/width ratio of ≥ 2.0, a depth of score line of ≥ 0.5 mm a resistance to crushing of ≤ 100 Newton will ensure an adequate ease of breaking. We advise that manufacturers rationalise tablet geometry with respect to shape, size and depth of the score mark. Further, we recommend updating the predictive models for scored tablets, especially by enlarging the sample size.

General discussion

Chapter 5, General discussion, summarises the main findings in this thesis and discusses the approaches and challenges in improving the user-friendliness of medicines for the relevant stakeholders that are involved in the development, evaluation, and prescription and dispensing of medicines. The stakeholders that we took into consideration in our discussion

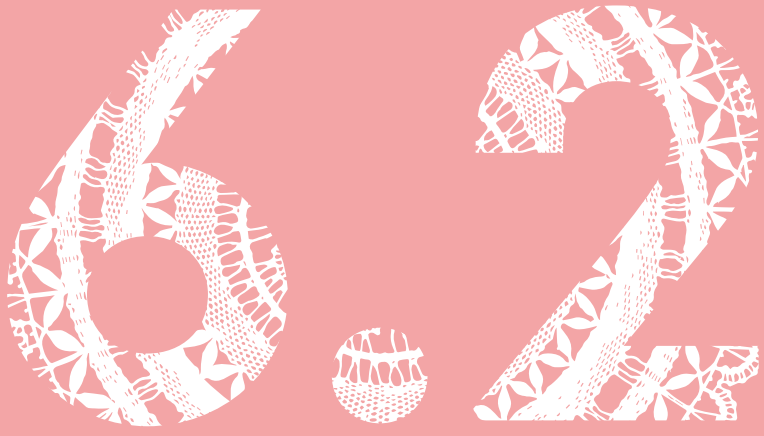
are medicines developers, regulators, health care professionals (particularly prescribers and pharmacists), health insurance companies and the users themselves.

We recommend that medicines developers evaluate the usability of medicines for the intended user population during product development, and include the outcomes of usability studies within the marketing authorisation application. Concomitantly, we advise regulators to encourage medicine developers to conduct usability studies and assess the outcomes of such studies as part of the marketing authorisation application. In addition, collecting and sharing post-marketing reports on usability problems with medicines could significantly contribute to the prevention of similar problems with other products. The development of tamper-evident and child-resistant closures that remain accessible for older people poses a challenge for product developers and designers. The prevalence of problems with the opening of tamper-verification features and child-proof closures will further increase as a consequence of the ageing of the population and the requirement for tamper-evident verification on all pharmaceutical packaging per February 2019. In addition, we recommend that regulators reconsider the use of score marks as well the current requirements for assessment of score mark performance.

Patients are not forthcoming about problems with the use of their medicines. The solutions that patients come up with themselves to overcome experienced problems demonstrate creativity and resourcefulness, however, patients are not aware when their solutions are suboptimal and lead to incorrect medication use with potentially clinically relevant consequences. Health care providers should therefore encourage patients to report their usability problems. Effective collaboration between general practitioners, specialists and pharmacists plays an important role in preventing and overcoming usability problems with medicines both in hospitals and in primary care. Physicians can ask patients about their experiences with the use of their medicines and proactively inform pharmacy staff about (potential) usability issues. We also recommend pharmacists and pharmacy technicians to ask patients about their experiences with the use of their medicines, and demonstrate and practice how to use the dispensed medicines. Further, it would be of added value to provide education to pharmacists and pharmacy technicians on addressing usability problems.

Health care insurance companies also play a role in preventing usability problems with medicines. It is recommended that patients are offered a choice between suppliers of prescription medicines so they can choose to use a product that fits their personal needs or preferences. Health insurers are also recommended to take the usability of a medicine into account when selecting preferred suppliers and be willing to pay a little bit extra when the benefits of a certain product are evident for an individual patient. In addition, co-payments could be installed if the product that the patient prefers exceeds a reference price. This will help to contain drug costs, but still gives patients more freedom of choice.

In conclusion, this thesis demonstrates that the user-friendliness of medicines can much be approved. It reveals the complexity of ageing and the use of medicines, which often requires a need for assistance or the use of kitchen tools. Where other markets have started developing products specifically for older people, such as smartphones and playing cards with large print, the development of medicines has stayed behind. Through the development of more user-friendly medicines, the self-use of medicines can be improved, leading to better compliance with a medication regimen and making daily life easier. This requires a multifaceted approach; not only medicine developers can contribute to the better use of medicines, also regulatory agencies, health care providers, health insurers and patients themselves should be committed to contribute to this.



Chapter 6.2

Samenvatting

Dit proefschrift gaat over de gebruiksvriendelijkheid van geneesmiddelen. Het gebruik van geneesmiddelen is een ingewikkeld proces waarbij allerhande problemen kunnen optreden, zoals met het openen van de verpakking, het in tweeën delen van tabletten of met het toedienen van oogdruppels. Dergelijke praktische problemen kunnen leiden tot het verkeerd gebruik van geneesmiddelen en een verslechtering van de gezondheid of ongewenste effecten ten gevolg hebben, variërend van ongemak tot serieuze reacties als ziekte of (her)opname in het ziekenhuis.

Het op de juiste manier gebruiken van geneesmiddelen hangt niet alleen af van de complexiteit van het gebruik van het middel, maar ook van het vermogen van de gebruiker om de noodzakelijke handelingen te kunnen uitvoeren. We kozen oudere mensen als uitgangspunt voor onze studies. Ouder worden gaat gepaard met een hogere prevalentie van ziekte en fysieke beperkingen, zoals beperkingen in zicht, gehoor, fijne motoriek en de kracht in de handen. Ouder worden kan zodoende de bekwaamheid van een patiënt om zijn of haar geneesmiddelen op de juiste manier te gebruiken beïnvloeden. Daarnaast vormen oudere mensen ook de grootse groep gebruikers van geneesmiddelen. Wanneer er tijdens de ontwikkeling van geneesmiddelen rekening gehouden wordt met de bekwaamheid van oudere personen, dan zullen zij hun geneesmiddelen langer zelfstandig kunnen blijven gebruiken. Tevens zal het ontwerpen van geneesmiddelen die gemakkelijk te gebruiken zijn door oudere mensen ook voordelen hebben voor populaties die vergelijkbare problemen met het gebruik van geneesmiddelen ervaren en zelfs diegene die geen beperkingen hebben zullen baat hebben bij meer gebruiksvriendelijkere geneesmiddelen.

Dit proefschrift bestaat uit drie delen. Hoofdstuk 2 beschrijft de praktische problemen die oudere patiënten ondervinden met het dagelijks gebruik van hun geneesmiddelen. De studies beschreven in hoofdstuk 3 beschrijven de geschiktheid van het ontwerp van geneesmiddelen voor gebruik door oudere mensen. Hoofdstuk 4 gaat over het voorkomen van gebruiksproblemen met geneesmiddelen. In hoofdstuk 5 worden de resultaten van de studies in dit proefschrift samengevat en in een breder perspectief geplaatst met als doel aanbevelingen voor het bevorderen van de gebruiksvriendelijkheid van geneesmiddelen te geven.

De ervaringen van oudere personen met geneesmiddelgebruik

Hoofdstuk 2 begint met een beschrijving van de resultaten van een telefonisch onderzoek dat is afgenomen bij 317 patiënten van 65 jaar of ouder waarbij gevraagd is naar de ervaringen met het gebruik van verpakkingen van omeprazol tabletten en capsules. Omeprazol tabletten en capsules zijn in Nederland verkrijgbaar in potten, doordruk blisters en afpelbare blisters, d.w.z. blisters waarvan de achterzijde moet worden opengetrokken. De studie liet zien dat ongeveer één op de vier patiënten één of meerdere problemen ervaart met het openen van omeprazol-verpakking. De meeste problemen kwamen voor met de afpelbare blisters; tweederde van de respondenten die deze verpakking gebruikten hadden moeite met het gebruik van dit type blister. Patiënten die omeprazol in een pot ontvangen melden de minste problemen met het openen van de verpakking. Tweederde van de patiënten gaf aan een oplossing gevonden te hebben voor de ervaren problemen. Toegepaste oplossingen zijn bijvoorbeeld hulp van partner, familie en buren, het gebruik van keukenhulpmiddelen en het overbrengen van de geneesmiddelen naar een andere verpakking. De bevindingen van deze studie laten zien dat de gebruiksvriendelijkheid van de verpakking van geneesmiddelen aanzienlijk verbeterd kan worden.

Hoofdstuk 2.2 gaat verder met onderzoek naar de gebruiksvriendelijkheid van zowel de verpakking als het geneesmiddel zelf. Dit hoofdstuk beschrijft de resultaten van een kwalitatief onderzoek naar het dagelijks gebruik van orale geneesmiddelen door oudere personen. Middels semigestructureerde interviews met 59 zelfstandig wonende mensen van 70 jaar of ouder hebben we informatie verzameld over de praktische problemen die oudere mensen ervaren met het gebruik van hun geneesmiddelen en de wijze waarop zij deze problemen oplossen. Deelnemers waren benaderd via een openbare apotheek en een geriatrische poliklinische afdeling in Utrecht en gebruikten dagelijks zelfstandig, minimaal drie verschillende orale receptplichtige geneesmiddelen. De interviews zijn bij de deelnemers thuis afgenomen, aan de hand van hun eigen medicatie. De deelnemers gebruikten gemiddeld 6.9 orale receptplichtige geneesmiddelen. In totaal zijn 211 problemen en 184 oplossingen gemeld. Een overgrote meerderheid (95%) van de deelnemers ondervond minstens één praktisch probleem bij het geneesmiddelgebruik, variërend van problemen met het lezen en begrijpen van de bijsluiter, de buitenverpakking, de binnenverpakking, het klaarmaken voor gebruik en de daadwerkelijke inname van het geneesmiddelen. Drie deskundigen beoordeelden de potentiële klinische gevolgen van de problemen en oplossingen. Bij 10 deelnemers (17%) bestond de kans dat ten minste een van de problemen

die ze ondervonden zou leiden tot verslechtering van de gezondheid, met een totaal van 11 potentieel klinisch relevante situaties. Vijfennegentig procent van de problemen worden niet als klinisch relevant beschouwd, maar veroorzaken echter wel ongemak. Deze studie laat zien welke verschillende problemen oudere personen kunnen ervaren met het gebruik van hun geneesmiddelen en wat de klinische gevolgen daarvan kunnen zijn. De bevindingen vormen een uitdaging voor zorgverleners, geneesmiddelontwikkelaars en registratie autoriteiten om manieren te vinden om de praktische problemen van ouderen te verminderen.

De geschiktheid van het ontwerp van geneesmiddelen voor gebruik door oudere personen

In hoofdstuk 3.1 hebben we de vaardigheid van oudere personen om tabletten met breuk-streep in tweeën te delen vergeleken met die van jong volwassen. Gezondheids-karakteristieken zoals perifere neuropathie, verminderde kracht in de handen en een verminderde motoriek kunnen de vaardigheid van een patiënt om tabletten te breken beïnvloeden. Omdat deze beperkingen geassocieerd zijn met ouder worden en aan ouderdom gerelateerde ziekten als Parkinson en Artritis, zouden problemen met het in tweeën delen van tabletten vaker kunnen voorkomen onder oudere mensen. Wij hebben de vaardigheid van 36 oudere personen en 36 jong volwassenen om 12 verschillende tabletten met breukstreep te breken onderzocht. Elk tablet werd gebroken op drie gangbare manieren om tabletten met de hand te breken; tussen de vingers zonder de nagels te gebruiken, tussen de vingers en met het gebruik van nagels, en door op de tablet te drukken terwijl deze op een stevig oppervlak ligt. De primaire uitkomstmaten waren het kunnen breken van de tabletten en het in twee gelijke helften kunnen breken van de tabletten, ofwel de accuraatheid van het breken. Het bleek dat de oudere personen significant meer moeite hadden om de tabletten te kunnen delen in vergelijking met de jong volwassenen. De oudere deelnemers braken gemiddeld 38,1% van de tabletten, waarvan 71.0% accuraat gebroken was. De jongeren braken gemiddeld 78,2% van de tabletten, waarvan 77.4% accuraat. Verdere analyse middels logistische regressie bevestigde dat leeftijd geassocieerd was met de vaardigheid om tabletten te kunnen breken (OR = 50,56; P < 0.001), maar niet met de het accuraat kunnen delen (OR = 1,19; P = 0,364). Problemen met het breekgemak van tabletten zijn niet alleen hinderlijk. Ze maken het medicatieregime ingewikkelder en verhogen daarmee het risico op therapieontrouw, medicatiefouten en bijwerkingen. De hoge prevalentie van problemen met het breken van tabletten in deze studie toont het belang aan deze problemen te reduceren. Zorgverleners dienen er bewust van te zijn dat

het breken van tabletten niet voor iedere patiënt en niet voor ieder geneesmiddel geschikt is. Wij concludeerden dat om een veilig gebruik van geneesmiddelen te waarborgen, het breken van tabletten door oudere patiënten vermeden dient te worden en alternatieven moeten worden overwogen.

Hoofdstuk 3.2 beschrijft ontwerpaspecten van orale geneesmiddelen die gebruiksproblemen bij oudere patiënten veroorzaken. Tijdens de kwalitatieve studie beschreven in hoofdstuk 2.2 is ook informatie verzameld over de ontwerpeigenschappen van de geneesmiddelen waarvoor de gebruiksproblemen werden gemeld, zoals het type geneesmiddel, de kleur, vorm, grootte, smaak, aanwezigheid van een filmlaag, aanwezigheid van een breukstreep, en type en eigenschappen van de verpakking van het geneesmiddel. We hebben daarbij onderscheid gemaakt tussen situaties waarbij de deelnemer moeite had met het gebruik van het geneesmiddel maar het wel lukte om het geneesmiddel zelfstandig en zonder hulpmiddel of andere strategie te gebruiken (moeilijkheden met het gebruik), en situaties waarbij de deelnemer assistentie nodig had of een hulpmiddel of andere strategie gebruikte om het geneesmiddel te gebruiken (gebruiksfouten). We hebben bepaald wat de bijdrage van de diverse ontwerpaspecten zijn aan het optreden van de moeilijkheden en fouten met het gebruik van de geneesmiddelen. In totaal zijn 158 gebruiksproblemen naar voren gekomen, waarvan er 45 zijn geclassificeerd als moeilijkheden en 113 als gebruiksfouten. Ontwerpeigenschappen die de meeste moeilijkheden met het gebruik veroorzaakten waren afmeting (29,6%) en oppervlakte-eigenschappen (18,5%) van het geneesmiddel. Gebruiksfouten werden het meest veroorzaakt door de kracht die nodig was om de middelen uit de blister te drukken (22,1%) en door verzegelde verpakkingen (12,1%). We concludeerden dat een meer op de patiënt gerichte ontwikkeling van geneesmiddelen het gemakkelijker en veiliger gebruik van geneesmiddelen zal bevorderen. We raden aan om mogelijke verbeteringen in het ontwerp van geneesmiddelen te onderzoeken middels ‘human factor’ en/of ‘usability engineering’, zoals al voor medische hulpmiddelen gedaan wordt.

Benaderingen om gebruiksproblemen met geneesmiddelen te voorkomen

De studie die wordt beschreven in hoofdstuk 4.1 onderzocht tot in welke mate apothekersassistenten problemen met het openen van verpakkingen signaleren en hoe ze deze problemen oplossen. We hebben een cross-sectionele studie met semigestructureerde vragenlijsten uitgevoerd onder 31 apothekersassistenten uit 31 apotheken. Hierbij hebben

we het voorkomen van gebruiksproblemen en de verschillende type gebruiksproblemen met geneesmiddelverpakkingen onderzocht, evenals de voorgestelde oplossingen. Dit onderzoek laat zien dat alle apothekersassistenten problemen met het gebruik van verpakkingen signaleren, maar dat patiënten deze zelden zelf aan de apotheekbalie melden. Niet alle assistenten waren bekend met de manier waarop alle verschillende type verpakkingen moeten worden open gemaakt, maar ze wisten wel de gebruikelijke oplossingen voor problemen met openen te beschrijven. Oplossingen die de apothekersassistenten suggereerden waren onder andere het bieden van informatie en begeleiding, de verpakking wijzigen of aanpassen en het aanbieden van hulpmiddelen. De conclusie van dit onderzoek was dat hoewel apothekersassistenten op de hoogte zijn dat geneesmiddelverpakkingen gebruiksproblemen kunnen veroorzaken en ze in staat zijn problemen te bieden voor de oplossingen, er in de meeste apotheken geen systematische aandacht is voor de verpakking van een geneesmiddel bij de uitgifte van medicijnen. We raden daarom aan dat het vragen naar mogelijke problemen met het gebruik van de verpakking een vast onderdeel wordt van de medicatiebegeleiding. Apothekers dienen de assistenten te aan te moedigen en te ondersteunen bij het geven van dergelijke begeleiding.

Hoofdstuk 4.2 beschrijft de ontwikkeling van in vitro procedures voor onderzoek naar het veilig kunnen innemen van vaste orale geneesmiddelen met een kleine portie voedsel om daarmee problemen met het slikken van het geneesmiddel te voorkomen. Ongeveer een derde van de algemene populatie ondervindt moeilijkheden met het slikken van tabletten en capsules, en deze problemen komen vaker voor bij oudere personen. Het slikken van tabletten en capsules kan worden vergemakkelijkt door deze gelijktijdig in te nemen met een lepel half-vast voedsel (zoals yoghurt, vla of appelmoes) of een speciaal hiervoor ontwikkelde gel. Dergelijke alternatieve manieren van het innemen van geneesmiddelen worden echter zelden in de productinformatie vermeld. Om deze te mogen opnemen dienen farmaceutische bedrijven de impact van de gelijktijdige toediening van het voedsel op de veiligheid en werkzaamheid van het betreffende geneesmiddel te verifiëren. Toezichthouders hebben aangegeven dat dit mogelijk is middels in vitro studies, er bestaan echter geen gestandaardiseerde methoden voor een dergelijk onderzoek. Om de opname van alternatieve methoden om het geneesmiddel in te nemen in de productinformatie te faciliteren, hebben we onderzocht of in vitro disintegratie en dissolutie methoden geschikt zijn als instrument voor het vaststellen van potentiele incompatibiliteit tussen vaste orale geneesmiddelen en kleine hoeveelheden voedsel. We hebben de effecten van 5 ml appelmoes, vanillevla, yoghurt en een gel op de desintegratie van carbamazepine tabletten, dabigatran etexilaat capsules, lithium carbonaat tabletten met directe als met verlengde afgifte en twee verschillende type paracetamol tabletten onderzocht, evenals het effect van deze voedingsmiddelen op de dissolutie van carbamazepine tabletten. De resultaten laat

zien dat de gelijktijdige toediening van paracetamol, carbamazepine en lithium carbonaat tabletten met directe afgifte met een lepel appelmoes, vanillevla, yoghurt en de gel een statistisch significante en product-afhankelijke vertraging in de desintegratiesnelheid veroorzaakt. Het onderzoek liet daarnaast ook zien dat de gelijktijdige toediening van carbamazepine tabletten met een lepel vanille vla, yoghurt en de gel een statistisch significante vertraging in de dissolutie van carbamazepine veroorzaakte. Deze studie suggereert dat in vitro methoden kunnen aanwijzen of het uitvoeren van verder onderzoek, zoals biostudies, noodzakelijk is. Er zijn echter meer gegevens van oplossnelheidsonderzoek met geneesmiddelen met verschillende desintegratie en dissolutie eigenschappen nodig. Met dit onderzoek willen we klinische onderzoekers stimuleren bij te dragen aan de ontwikkeling van in vitro evaluatietools doormiddel van het uitvoeren van in vitro studies naast de huidige in vivo studies.

In hoofdstuk 4.3 hebben we de prestatie van een eerder ontwikkeld model dat het breekgemak van ovale en ronde tabletten met breukstreep voorspeld aan de hand van de fysieke tablet kenmerken. Dit statistisch model is ontwikkeld met behulp van daadwerkelijk bevindingen voor het breken van tabletten door een testgroep en voorspelt de proportie mensen die een specifiek tablet kunnen breken. Dit model kan een waardevol instrument zijn voor de evaluatie van het functioneren van een breukstreep tijdens de ontwikkeling van tabletten. We hebben de voorspellende prestatie van het model voor ovale en voor ronde tabletten onderzocht door het voorspelde breukgemak te vergelijken met de daadwerkelijke bevindingen van een testgroep (n=36). De resultaten voor de ronde tabletten laten zien dat de waargenomen en voorspelde waarden niet goed overeenkomen. Het onvoldoende voorspellend vermogen kan worden verklaard door de geringe omvang van de steekproef voor de ontwikkeling van het model, maar ook door mogelijke verschillen tussen de deelnemers, de setting en de tabletten gebruikt in de studie voor de ontwikkeling van het model en onze studie. Voor de ovale tabletten heeft het model de werkelijke bevindingen onderschat. Dit komt overeen met de opmerking gemaakt door de onderzoekers die het model ontwikkeld hebben dat de criteria voor de ovale tabletten conservatief zijn opgesteld. We concludeerden dat het model voor de ronde tabletten momenteel onvoldoende betrouwbaar is om te worden toegepast tijdens de ontwikkeling van tabletten. Echter, ovale tabletten die voldoen aan de volgende eigenschappen zijn voldoende gemakkelijk te breken: lengte van ≥ 10 mm, een lengte/breedte ratio van ≥ 2.0, diepte van de breukstreep ≥ 0.5 mm en een breekweerstand van ≤ 100 Newton. We raden geneesmiddelfabrikanten aan om bij het ontwikkelen van tabletten met een breukstreep de geometrie van een tablet, waaronder vorm, grootte en de diepte van de breukstreep, te rationaliseren. Daarnaast zou het van toegevoegde waarde zijn de modellen voor tabletten met een breukstreep verder te ontwikkelen, voornamelijk door de steekproef uit te breiden met meer tabletten.

Algemene beschouwing

In de algemene beschouwing, hoofdstuk 5, zijn de bevindingen van onze studies samengevat en bespreken we de mogelijkheden en uitdagingen voor het verbeteren van de gebruiksvriendelijkheid van geneesmiddelen voor de relevante stakeholders die zijn betrokken bij de ontwikkeling, evaluatie, het voorschrijven en afleveren van geneesmiddelen. We hebben in onze beschouwing aandacht besteed aan geneesmiddelontwikkelaars, regelgevers, zorgverleners (in het bijzonder voorschrijvers en apothekers), zorgverzekeraars en de gebruikers zelf.

We raden aan dat geneesmiddelontwikkelaars de gebruiksvriendelijkheid van geneesmiddelen voor de beoogde populatie onderzoeken gedurende de productontwikkeling en de resultaten van usability-onderzoek opnemen in het registratiedossier. Tegelijkertijd adviseren we dat toezichthouders geneesmiddelontwikkelaars aanmoedigen om usability-onderzoeken uit te voeren en de uitkomsten van een dergelijk onderzoek te beoordelen als onderdeel van de registratie-aanvraag. Daarnaast zal het verzamelen en delen van post-marketing meldingen met gelijksoortige geneesmiddelen een significante bijdrage leveren aan het voorkomen van vergelijkbare problemen bij andere middelen.

De ontwikkeling van verzegelde verpakkingen en kindveilige sluitingen die wel gemakkelijk te openen blijven voor ouderen vormt een uitdaging voor productontwikkelaars en ontwerpers. De hoeveelheid problemen met het openen van verzegelde verpakkingen en kindveilige sluitingen zullen als gevolg van de vergrijzing van de samenleving toenemen, maar ook omdat alle verpakkingen vanaf februari 2019 voorzien dienen te zijn van een verzegelde verpakking. We adviseren de toezichthouders ook om de toepassing van breukstrepen te heroverwegen, evenals de eisen voor de beoordeling van het functioneren van breukstrepen.

Patiënten geven niet snel aan dat ze problemen met het gebruik van geneesmiddelen ervaren. Patiënten ontwikkelen creatieve en vindingrijke strategieën om gebruiksproblemen te voorkomen, echter, ze zijn zich er niet van bewust wanneer de oplossingen die ze hanteren suboptimaal zijn en leiden tot verkeerd gebruik van geneesmiddelen met mogelijk klinische relevante gevolgen. Zorgverleners dienen patiënten daarom aan te moedigen gebruiksproblemen kenbaar te maken. Een effectieve samenwerking tussen huisartsen, specialisten en apothekers speelt een belangrijke rol in het vorkomen en omgaan met gebruiksproblemen met geneesmiddelen, zowel in de ziekenhuisomgeving als in de eerstelijnszorg.

Artsen kunnen patiënten vragen naar hun ervaringen met het gebruik van hun middelen en kunnen apotheekmedewerkers proactief informeren over (potentiele) gebruiksproblemen.

We raden tevens aan dat apothekers en apotheekassistenten patiënten vragen naar hun ervaringen met het gebruik van hun geneesmiddelen, en demonstreren en oefenen hoe ze hun medicijnen dienen te gebruiken. Het is daarnaast van toegevoegde waarde om apothekers en apotheekassistenten training te bieden om gebruiksproblemen aan te kunnen pakken.

Zorgverzekeraars spelen ook een rol in het voorkomen van gebruiksproblemen met geneesmiddelen. Patiënten zouden een keus moeten hebben tussen de verschillende aanbieders van receptplichtige geneesmiddelen zodat ze kunnen kiezen voor een product dat aansluit bij hun persoonlijke behoefte en voorkeur. We raden zorgverzekeraars ook aan om de gebruiksvriendelijkheid van een geneesmiddel mee te wegen bij het selecteren van preferente aanbieders en bereid te zijn hier extra voor te betalen wanneer de voordelen voor een individuele patiënt evident zijn. Ook kan een bijbetaling gehanteerd worden wanneer een patiënt voorkeur geeft aan een middel dat een hogere prijs heeft dan de referentieprijs. Zodoende kunnen de kosten van geneesmiddelen in de hand gehouden worden terwijl patiënten tegelijkertijd meer keuzevrijheid genieten.

Dit proefschrift laat zien dat de gebruiksvriendelijkheid van geneesmiddelen aanzienlijk verbeterd kan worden. Het laat de complexiteit zien van het ouderen worden in combinatie met het gebruik van geneesmiddelen, waarbij dikwijls assistentie nodig is of keukenhulpmiddelen gebruikt worden. Daar waar andere markten producten afgestemd op gebruik door ouderen zijn gaan ontwikkelen, zoals mobiele telefoons en speelkaarten met grote print, is de ontwikkeling van geneesmiddelen achtergebleven. Door het ontwikkelen van meer gebruiksvriendelijke geneesmiddelen zal het zelfstandig gebruik van geneesmiddelen bevorderd worden, wat zal leiden tot een betere therapietrouw en het dagelijks leven gemakkelijker maakt. Hier is een gezamenlijke inspanning voor nodig; niet alleen geneesmiddelontwikkelaars kunnen bijdrage aan een beter gebruik van geneesmiddelen, maar ook regelgevers, zorgverleners, zorgverzekeraars en patiënten zelf dienen zich in te zetten om hier een bijdrage aan te leveren.

Chapter 7

Addendum

7.1

Chapter 7.1

Dankwoord

Grotendeels onwetend over wat me precies te wachten stond, begon ik in januari 2011 met mijn promotieonderzoek. Nu, ruim zes jaar later, kijk ik met plezier én trots terug op een bijzondere periode in mijn leven. Een periode waarin ik veel heb geleerd, niet alleen van het onderzoek maar van de hele weg tot aan de verdediging van dit proefschrift toe. Graag bedank ik iedereen die mij heeft begeleid, gemotiveerd en geholpen. Een aantal personen wil ik in het bijzonder bedanken.

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7.2

Chapter 7.2

List of publications

Related to this thesis

Notenboom K, Leufkens HGM, Vromans H, Bouvy ML. Learning from Patients: Identifying Design Features of Medicines that Cause Medication Use Problems. Int J Pharm. 2017;517(1-2):128-134

Notenboom K, Vromans H, Schipper M, Leufkens HGM, Bouvy ML. Relationship between age and the ability to break scored tablets. Front Pharmacol. 2016 Jul;7:222

Notenboom K, Beers E, van Riet-Nales DA, Egberts ACG, Leufkens HGM, Jansen PAF, Bouvy ML. Praktische problemen die ouderen ervaren met het gebruik van hun geneesmiddelen Ins&Ouds 2015(3):22-26

Notenboom K, Beers E, van Riet-Nales DA, Egberts ACG, Leufkens HGM, Jansen PAF, Bouvy ML. Ouderen krijgen tablet of capsule moeilijk uit blister. Pharm Weekblad 2015;150(39):12-14

Notenboom K, Beers E, van Riet-Nales DA, Egberts ACG, Leufkens HGM, Jansen PAF, Bouvy ML. Practical problems with medication use that older people experience: a qualitative study. J Am Geriatr Soc. 2014 Dec;62(12):2339-44

Philbert D, **Notenboom K**, Bouvy ML, van Geffen EC. Problems experienced by older people when opening medicine packaging. Int J Pharm Pract. 2014 Jun;22(3):200-4

Philbert D, **Notenboom K**, Kosters ES, Fietjé EH, van Geffen EC and Bouvy ML. Pharmacy technicians' attention to problems with opening medicine packaging. J Pharm Technol. 2014 Feb;30(1):3-7

Unrelated to this thesis

Peter M.J.M. Jongen, Cornelis A. van den Bogert, Catharina W.E. van de Laar, Kim Notenboom, Elysée T.M. Hille, Ingrid Hegger. Risk indicator taxonomy for supervision of clinical trials on medicinal products. Curr Med Res Opin. 2016 Jul;32(7):1269-76

van Riet-Nales DA, Doeve ME, Nicia AE, Teerenstra S, **Notenboom K**, Hekster YA, van den Bemt BJF. The accuracy, precision and sustainability of different techniques for tablet subdivision: breaking by hand and the use of tablet splitters or a kitchen knife. Int J Pharm. 2014 May 15;466(1-2):44-51.

7.3

Chapter 7.3

About the author

About the author

Kim Notenboom was born on the 25th of June 1976 in Eindhoven, the Netherlands. She studied Pharmaceutical Sciences at Utrecht University. As part of her study she completed a 9-month research internship at the Department of Pharmacology of the University of Western Cape in Bellville, South-Africa. During her study, she worked in several community pharmacies. After she obtained her degree in 2004, Kim worked for four years in the pharmaceutical industry, principally in the area of regulatory affairs. In 2008 Kim started working for the National Research Institute for Public Health and the Environment (RIVM) in Bilthoven as a scientist/chemical-pharmaceutical assessor. As an assessor, Kim has been involved in the World Health Organisation Prequalification Programme since 2009. In 2011, Kim started her PhD project on user-friendly medicines. The project was a collaboration of RIVM's Strategic Research programme and Utrecht University. In the same year, the assessors' department of the RIVM was incorporated into the Dutch Medicines Evaluation Board (MEB). Kim combined her PhD project with a position as a scientist/project leader at the RIVM and a part-time position at the MEB as a chemical-pharmaceutical assessor. Kim became full-time employed at the MEB in 2016. In 2017, Kim worked for 6 months as a technical officer at the World Health Organisation Prequalification Programme in Geneva. Kim now works as a senior chemical-pharmaceutical assessor at the MEB. Kim lives together with Pank van 't Hoog in Utrecht.