

The frequency of inappropriate tablet splitting in primary care

R. Quinzler · C. Gasse · A. Schneider ·
P. Kaufmann-Kolle · J. Szecsenyi · W. E. Haefeli

Received: 21 March 2006 / Accepted: 16 August 2006
© Springer-Verlag 2006

Abstract

Introduction We assessed the frequency and determinants of tablet splitting in primary care in Germany and evaluated the quality of information on divisibility in the Summary of Product Characteristics (SPCs) and in the Package Leaflet (PL) as legal sources of information for health care providers and patients.

Methods We performed a cross-sectional questionnaire survey among patients of 59 general practitioners in the German Federal State Saxony-Anhalt in 2005 in order to collect detailed information on all drugs of patients maintained on more than three drugs.

Results The response rate was 82.1% ($n=905$) and 3,158 drugs (tablets and dragées) were included in the analyses. Of all drugs, 24.1% were split (762 of 3,158): 8.7% of all split tablets were unscored (66 of 762) and 3.8% of all split tablets were not allowed to be split (29 of 762). Tablets of

the higher price categories and higher strengths were twice as likely to be split. Only 22.5% of the SPCs (9 of 40) of the split unscored tablet brands contained explicit information on divisibility and only 36.4% of the PLs (8 of 22) of the split brands that were not allowed to be split stated that splitting was not appropriate.

Conclusion The splitting of tablets in primary care is a frequent habit likely driven by medical and economic considerations. Almost 1% of all tablets are split that must not be fragmented. However, the SPC and PL provide only limited information on divisibility stressing the need to improve this information promptly to avoid medication errors.

Keywords Package leaflet ·
Summary of product characteristics · Survey ·
Tablet splitting

R. Quinzler · C. Gasse · W. E. Haefeli (✉)
Department of Internal Medicine VI,
Clinical Pharmacology and Pharmacoepidemiology,
University of Heidelberg,
Im Neuenheimer Feld 410,
69120 Heidelberg, Germany
e-mail: walter.emil.haefeli@med.uni-heidelberg.de

A. Schneider · J. Szecsenyi
Department of General Practice and Health Services Research,
University of Heidelberg,
Heidelberg, Germany

P. Kaufmann-Kolle
AQUA-Institute for Applied Quality
Improvement and Research in Health Care,
Göttingen, Germany

Present address:

C. Gasse
Klinisk Epidemiologisk Afdeling, Århus Universitetshospital,
8000 Århus C, Danmark

Introduction

Tablets are frequently split by patients on oral drug therapy [1], a procedure which may provide several advantages. A major benefit is to achieve dose flexibility to account for the considerable interindividual differences in dose requirements, for instance, in paediatric and geriatric patients, for whom appropriate strengths are often not available on the market [2, 3]. It may also happen that drugs have been identified as beneficial in indications other than those approved by the authorities (off label use) and at lower doses than the available strengths, making tablet splitting an essential safety step in such regimens. A pertinent example is the treatment of congestive heart failure with spironolactone, which results in excessive toxicity when intact tablets (whose strength in most cases exceeds the recommended 25 mg) are taken [4]. Moreover, drug–drug interactions [5] or genetic variants (e.g. poor metaboliser

tatus of cytochrome P450 isozymes; [6]) may result in substantially reduced dose-requirements demanding the prescription of liquid formulations or split tablets. In addition, some patients may break large-sized tablets to facilitate swallowing [2]. Finally, another likely reason for tablet splitting in Germany and elsewhere is the prescription of fragments of tablets with higher strength, in the frequent cases when unit prices increase less than dose proportionally with increasing strength [7–9]. In these cases, treatment costs may be reduced by 30% (e.g. Pravastatin-CT), up to almost 45%, as, e.g., in the treatment with molsidomine (e.g. Molsihexal 2 mg or Corvaton) [10]. For all these reasons, splitting of tablets is likely to be an essential part of today's drug treatment. However, not all tablets (and particularly not unscored tablets) are suitable for splitting. Splitting of extended release formulations can result in toxicity by uncontrolled release of the active ingredient, or the active ingredient can be destroyed when patients split enteric-coated formulations. A Dutch study [1] showed that patients even divide tablets without a score line. It was suggested that one reason could be the lack of information on the presence of score lines during the prescription process. For physicians and pharmacists, such information is expected to be found in the Summary of Product Characteristics (SPC) which forms the legal basis of prescribing and acts as the primary source of drug information for general practitioners (GPs) in Germany [11]. For patients, the Package Leaflet (PL) is the main source of information that should also provide essential information about the appropriate application of a drug.

The aim of this study was to assess the frequency and determinants of tablet splitting in primary care in Germany and to find out whether drugs actually split are indeed suitable for splitting. We also aimed to assess for all split drugs that are not suitable for splitting whether a switch to alternative drugs was possible. We further evaluated the impact on treatment costs that would have emerged if tablets of lower strength had been prescribed. Finally, we aimed to evaluate the quantity and quality of corresponding information available for physicians in SPCs and for patients in PLs.

Methods

Study population and setting

We performed a questionnaire survey in the German Federal State Saxony-Anhalt (Sachsen-Anhalt) between April and July 2005 among patients of GPs who participated in quality circles on rational prescribing [12]. Fifty-nine GPs in 54 practices agreed to hand out a questionnaire to up to 30 patients older than 18 years who used at least three medications. In the questionnaire, patients were asked to list all medications which they were actually taking

including over-the-counter (OTC) medication that they had obtained without prescription. In particular, they were requested to fill in the brand name of the drugs, the strength, the “Pharmazentralnummer” (PZN; a unique number that defines each marketed package), and the exact dosage regimen. In addition, patients were asked whether they ever have had problems with the exact division of tablets and, if so, how they solved these problems.

Participating patients were requested to send the questionnaire back to the study centre in a prepaid envelope. To increase the response rate, general reminder cards were sent to the patients by the participating practices and 3×250 EUR were raffled among respondents. To assess the response rate of the questionnaires, GPs were requested to list age and gender of all patients who received a questionnaire and to send this list to the study centre. The response rate was calculated as the number of returned questionnaires divided by the number of patients on the GPs' lists.

All returned questionnaires were included in the data analysis. The questionnaires were scanned by Eyes & Hands Forms version 5 (Trax UK, Rochester, United Kingdom) and the data was imported into SAS 9.13 (SAS Institute, Cary, N.C., USA). Supported by the phonetic and error tolerant search engine of our hospital drug information system *AiDKlinik* [13], we linked all PZNs or drug names to the database on the drugs marketed in Germany [10]. Drugs without PZN or with an incorrect PZN were manually processed and a PZN was assigned whenever the brand name and strength of the drug was correctly mentioned and a classification was unequivocally possible. If a classification was not possible, we excluded the drug. In a second step, all drugs with galenics other than tablets and dragées (for example liquids, inhalers, capsules) were excluded, and we also removed drugs with incomplete dosage information.

Assessment of splitting

We assessed splitting of tablets from the patients' dosage information. Whenever the patients stated in the dosage schedule that they took a fragment of a tablet (e.g., a half, or one-and-a half) we assumed that they split the tablet.

Assessment of divisibility

For the assessment of divisibility, we used the “Gelbe Liste-Pharmindex”-database [10] as a primary information source or obtained the respective information from the marketing authorisation holder of the drug in cases without such information in the data base. For all unscored tablets that were indicated by the patients as split tablets, we obtained additional information from the marketing authorisation holder. We characterised tablets without a score

line as “not suitable for splitting” and drugs without a score line that must not be split according to information from the marketing authorisation holder (e.g. extended release formulations) were characterised as “not allowed to split”.

Assessment of possibility to switch to alternative drugs

For all unscored split tablet brands, we evaluated whether a switch to more suitable brands was possible. Therefore, we checked whether a liquid formulation, a generic drug with a score line (and identical pharmaceutical form, active ingredient, and strength), or a drug with half the strength (but with the same pharmaceutical form and the same active ingredient) was available. If several alternative brands were available we selected the cheapest brand by comparing the unit prices of the largest marketed package sizes.

Assessment of unit prices

We obtained the prices and the packaging size of each drug from the “Gelbe Liste-Pharmindex”-database [10]. For the calculation of the unit prices, we divided the price of each package by the number of tablets per package.

Evaluation of SPC and PL

We screened all SPCs and PLs of the unscored split tablets for information on divisibility and a description of the visual appearance of the product. We classified tablets as divisible if the intake of a split single dose was recommended or if it was clearly indicated that the tablets may be divided. We classified tablets as not allowed to be split either if it was stated that the tablets must not be broken or if it was recommended to take the tablets undivided.

Statistical analysis

The patient characteristics (age, drugs per patient) are reported as mean \pm SD, and the percentage change in medication costs is expressed as median, minimum, and maximum. For the assessment of an association between tablet splitting and unit prices, we used a logistic regression model. The unit prices were divided into four categories, using the 25% percentile, the median, and the 75% percentile of the unit prices as limits, and dummy variables were constructed. We adjusted for the presence of a score line and the strength of a brand with the lowest strength being the reference group. The results are presented as unadjusted and adjusted odds ratios (OR), as an estimate of the relative risk, and 95% confidence intervals (CIs). The correlation of polypharmacy with tablet splitting was assessed with linear regression. All data were analysed using SAS 9.13 (SAS Institute).

Results

Study population

Altogether 1,770 questionnaires were sent to the 59 participating GPs (30 questionnaires to each GP) for distribution to eligible patients, and 905 patients sent their questionnaires back. The response rate was 82.1%. Of the responding 905 patients, 882 (97.5%) completed the medication list and only those were used for further analyses. 53.7% of the patients were women, the mean (\pm SD) age of the patients was 67.3 years (\pm 9.80), and the mean number of drugs per patient was 6.3 (\pm 2.6). The total number of drugs reported in the questionnaires was 5,543 (Fig. 1). We excluded drugs that could not be classified, because the patients did not fill in the correct PZN and also the brand name and strength of the drug was not unequivocally mentioned ($n=669$), and formulations other than tablets or dragées, e.g. inhaled sprays, ointments, capsules, and liquids ($n=725$). We also excluded 991 tablet formulations because the dosage regimen was incomplete or equivocal, i.e. dosage information was absent for 265 tablets [most of them were tablets taken PRN (as needed)] and in 726 cases the patients inserted an x instead of the exact number of tablets taken. Hence, 3,158 drugs with complete dosage information were included in the analysis.

Frequency of and problems related to tablet splitting

The frequency of tablet splitting is shown in Fig. 2. Of all tablet formulations, 24.1% were split (762 of 3,158). Of the split tablets, 8.7% (66 of 762; including 40 different brands) were not suitable for splitting because they did not have a score line, and 3.8% (29 of 762; including 22 different brands) were not allowed to be split, not even with a tablet splitter according to information from the marketing authorisation holder. The active ingredients of the most frequently split tablets are shown in Table 1. The listed active ingredients represent 50.1% of all split tablet packages (382 of 762) and 28.1% of all tablet packages (886 of 3,158). The available strengths for each active ingredient and the number of tablets that were split because of a dosage regimen with alternating doses are also listed in Table 1. The characteristics of the 29 unscored split drugs that were not allowed to be split are shown in Table 2.

A switch to more suitable drugs was possible in 25 of the 40 split unscored brands (62.5%): in seven cases (17.5%) it was possible to switch to generic alternatives with a score line, in 14 cases (35.0%) tablets with half the strength of the split formulation were available, in four cases (10.0%) both, switching to scored and half dosed tablets was possible, and in no instance a liquid formulation was available. Figure 3 shows the impact of switching on

Fig. 1 Selection procedure of study drugs of 882 ambulatory patients. For the assessment of the frequency of tablet splitting, we included 3,158 tablet formulations from the patients' medication data with complete dosage information and unequivocal classification

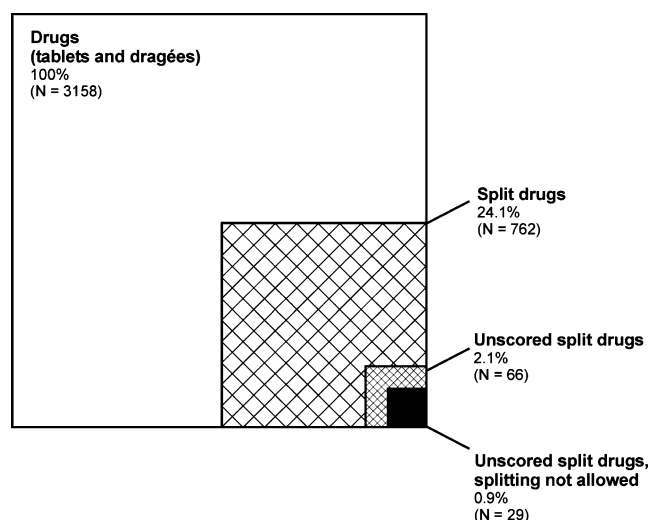
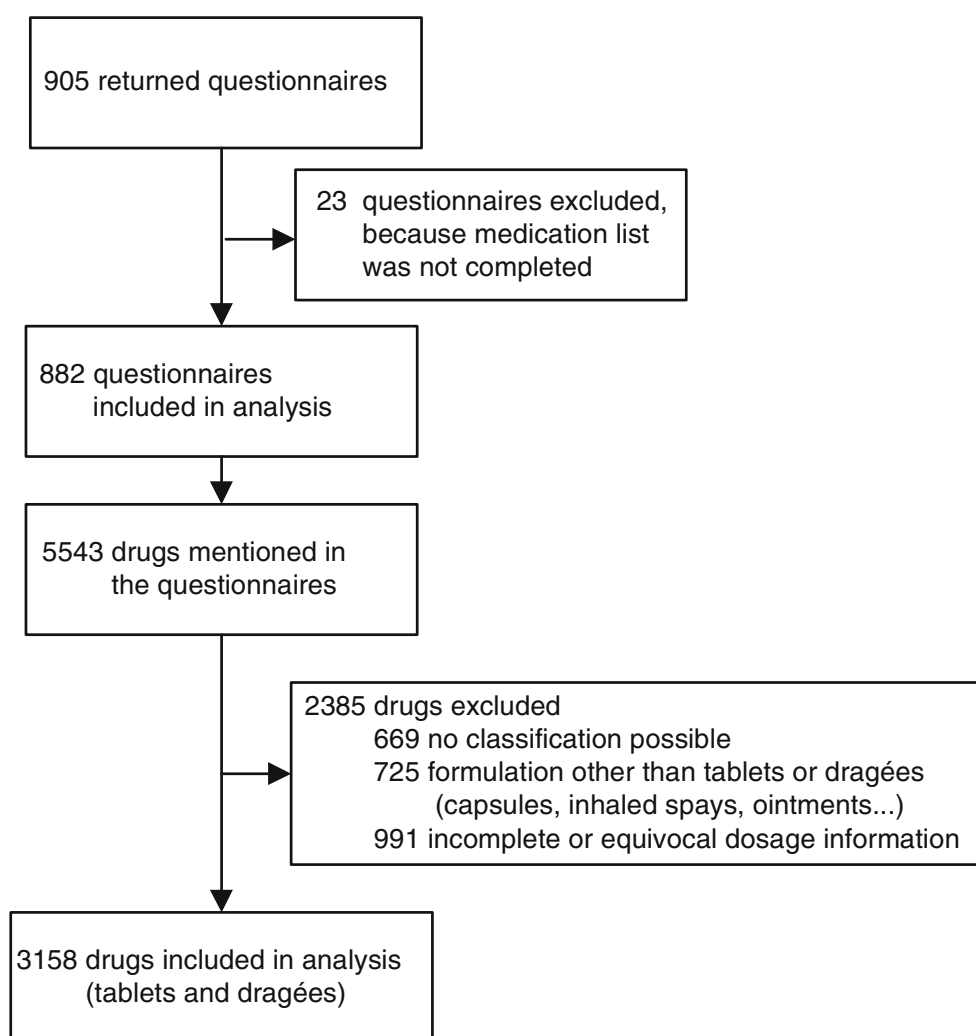


Fig. 2 Frequency of tablet splitting in 882 ambulatory patients. A total of 3,158 solid oral formulations were analysed. 24.1% of all drugs were split (762 of 3,158) and 66 drugs of all split drugs were unscored and therefore not suitable for splitting. Twenty-nine drugs of the unscored split drugs (3.8% of all split drugs) were not allowed to split according to information from the marketing authorisation holder

drug costs for the 25 unscored split brands for which an alternative was available. If the physicians had always selected the cheapest alternative, this would have resulted in a median increase in medication costs of +40.9% (range: -45.9% to +68.0%). However, in eight cases (32%), the drug cost would be reduced if the physician had switched to the cheapest comparable brand with a score line.

Table 3 summarises the associations between drug characteristics and splitting. Tablets with higher unit prices and higher strengths were twice as likely to be split and tablets with a score line were four times more frequently split.

Of our study population, 432 patients (49.0%) split at least one drug, 65 patients (7.4%) split unscored tablets, and 29 patients (3.3%) split tablets that were not allowed to split. A total of 144 of our 882 patients reported that they previously had problems with the exact division of tablets. The majority of these patients ($n=101$; 70.1%) reported that they solved the problem by using a knife or another sharp object. Only 28 (19.4%) patients reported that they had used a tablet splitter to solve this problem, 17 (11.8%) patients got help from other persons, and 4 patients (2.8%)

Table 1 Frequency of tablet splitting

Active ingredient	Total number of drugs	No. of split drugs (%)	No. of split drugs with alternating dosages ^a (%)	Available strengths in mg (no. of prescribed drugs/no. of split drugs)						
Metoprolol tartrate	103	57 (55)	4 (7)	50 (9/2) ^b 50 (18/8)	100 (19/8) ^b 100 (20/11)	200 (37/28) ^b				
Spirolactone	21	11 (52)	0 (0)	25 (4/1)	50 (14/8)	100 (2/2)				
Phenprocoumon	72	35 (49)	1 (3)	1.5 (0/0)	3 (72/35)					
Bisoprolol	60	29 (48)	3 (10)	2.5 (2/1)	5 (36/14)	10 (22/14)				
Carvedilol	53	25 (47)	4 (16)	6.25 (5/1)	12.5 (19/10)	25 (29/14)				
Atorvastatin	32	14 (44)	0 (0)	10 (14/6)	20 (12/7)	40 (6/1)				
Torasemide	76	32 (42)	7 (22)	2.5 (3/0)	5 (8/3)	10 (56/21)	20 (6/6)	200 (3/2)		
Captopril	41	17 (42)	2 (12)	12.5 (8/0)	25 (11/5)	50 (19/9)	75 (1/1)	100 (2/2)		
Lisinopril	32	13 (41)	5 (38)	2.5 (0/0)	5 (8/5)	10 (14/4)	20 (10/4)			
Pravastatin	32	13 (41)	0 (0)	10 (4/0)	20 (12/4)	40 (17/9)				
Simvastatin	101	39 (39)	0 (0)	5 (1/0)	10 (13/3)	20 (50/18)	30 (8/1)	40 (27/17)	80 (2/0)	
Metoprolol succinate	87	33 (38)	7 (21)	23.8 1(2/0) ^b	47.5 (35/12) ^b	95 (43/19) ^b	190 (7/2) ^b			
Ramipril	70	26 (37)	1 (4)	2.5 (12/2)	5 (31/9)	7.5 (1/1)	10 (26/14)			
Hydrochlorothiazide	30	11 (37)	0 (0)	12.5 (1/0)	25 (29/11)					
Candesartan	25	9 (36)	2 (22)	8 (10/2)	16 (13/5)	32 (2/2)				
Enalapril	51	18 (35)	2 (11)	2, 5 (2/0)	5 (15/4)	10 (16/5)	20 (18/9)			

Included are all brands with active ingredients that were most frequently split and prescribed at least 20 times in our study population.

^a E.g. one tablet in the morning and half a tablet in the evening

^b Extended release formulations

reported that they switched to other tablets, which they did not have to split. The number of tablets that were split was weakly correlated with the number of tablets prescribed to a patient ($r^2=0.163$; $p<0.001$).

Information in SPC and PL

The SPC provided only limited information to assess the divisibility of the unscored split tablets. Only 9 SPCs (22.5%) of the 40 different brands contained explicit information about the divisibility of the tablets and 19 of the remaining 31 SPCs described the shape of the tablets and thus indirectly informed physicians that the prescribed tablets are unscored. Hence, in 12 of 40 SPCs (30%) there was no information at all to inform the physician whether the tablets may be split or have a score line.

Even for the 22 preparations that were not allowed to be split information was limited. Only 8 of 22 SPCs (36.4%) mentioned that splitting was not allowed and only 8 of the 22 PLs contained information about the divisibility of the tablets. Hence, in only 8 instances (36.4%) could the patients have recognised that splitting was not appropriate.

Information on divisibility in SPCs of extended release formulations

Because we only assessed the data of a regional network, to obtain evidence on general information of the quality of

SPCs across the whole drug market, we also evaluated three active ingredients which are usually prescribed as a slow release formulation, are widely used, and off patent (i.e. available as generic formulations from numerous pharmaceutical companies). The divisibility of extended release formulations depends on the galenics of the tablets, and therefore explicit information on divisibility is needed to decide whether an extended release brand may be divided or not. Hence, we selected the SPCs of all available generic extended release tablets marketed in Germany that contain molsidomine 8 mg, metoprolol tartrate 200 mg, or felodipine 10 mg. All together 71 different brands were selected (molsidomine $n=13$, metoprolol tartrate $n=42$, and felodipine $n=16$). All SPCs of felodipine and all but one of the different metoprolol brands contained information on divisibility. In contrast, only 8 SPCs (61.5%) of the 13 different molsidomine brands contained information on the divisibility of the extended release tablets. Four of the molsidomine brands were not allowed to be split according to information from the marketing authorisation holder. In contrast, no SPC of these brands contained information on the divisibility of the tablets. More remarkable however, is that three of the molsidomine brands that were not allowed to be split were scored, which is misleading and could prompt a false assessment of the divisibility as evidenced by the fact that in our study population one of these two brands was 12 times prescribed and split in 5 cases (41.7%).

Table 2 Active ingredients and reasons that precluded safe splitting of the 29 unscored split drugs that were not allowed to split according to information from the marketing authorisation holder

Active ingredient	No. of drugs	Reasons that preclude safe splitting
Metoprolol	6	Galenic restrictions: extended release formulation
Molsidomine	6	Galenic restrictions: extended release formulation
Telmisartan	3	Hygroscopic properties of the active ingredient
Felodipine	2	Galenic restrictions: extended release formulation
Fluvastatin	2	Galenic restrictions: extended release formulation
Olmesartan	2	Unsavory taste; shape inappropriate for tablet splitter
Acetylsalicylic acid	1	Galenic restrictions: enteric coated tablet
Indapamide	1	Galenic restrictions: extended release formulation
Magnesium aspartate	1	Not disclosed
Metformin	1	Unsavory taste
Moxonidine	1	Unscored tablet with small diameter and extremely small amount of active ingredient
Oxycodone	1	Galenic restrictions: extended release formulation
Tolbutamide	1	Not disclosed
Valsartan combined with diuretics	1	Not disclosed

Discussion

Our study revealed that the dosing regimen of almost every second ambulatory German patient demands splitting of the medication before ingestion, and that, with almost 1% of all solid formulations, an important fraction is split that must not be fragmented. Hence, in about 3% of our patients, tablet splitting may result in an unintended change or even failure of drug response.

The frequency of splitting is in accordance with a small Dutch study, which was performed in five community pharmacies and revealed that 31% of 275 tablet prescriptions were split before swallowing. Similar to our study (8.7%), 11% of the split drugs in the Dutch study were also unscored [1]. While some of the unscored split tablets may be split with a tablet splitter, in our study population galenic restrictions in 43.9% (29 of 66 unscored drugs) precluded safe splitting.

The splitting of tablets may lead to unequal fragmentation, because many score lines currently lead to poorly reproducible splitting results [1, 14, 15], and because many

patients are unable to split even scored tablets [16]. Earlier studies indicate that ambulatory patients still rarely use tablet splitters to facilitate splitting [17]. Also in our study population, less than 20% reported that they use a tablet splitter when they had problems in splitting their tablets. Unequal fragmentation may lead to a number of problems in pharmacotherapy. First, it may increase the variability of the concentration-time profile, which may be relevant for drugs with narrow therapeutic ranges and relatively short half-lives with respect to the dosing interval. Second, it will reduce total exposure with the compound over time because of the loss of substance during the splitting procedure [2]. This may lead to losses of up to 24% when tablets are broken into quarters [18], which are expected to cause exposure changes beyond the generally accepted bioequivalence limit of -20%. Third, it may also increase costs because during the splitting procedure, multipart fragmentation may occur and some tablets may have to be discarded, as reported by 9% of the patients in a study in the USA [19].

Assuming that the splitting behaviour in our population was similar to the habits in Germany, irrespective of age and the number of drugs the patients are taking, we estimated the number of packages that are split in 1 year in the German population for drugs of the therapeutic class with the largest impact in chronic treatment. Hence, we selected beta blocking agents, calcium channel blockers, and agents acting on the renin-angiotensin system of which 52.6 Mio packages have been prescribed in Germany in 2004 [20]. Extrapolation of the results of our population reveals that in 2004, patients in Germany split tablets of approximately 16 Mio packages containing these agents. We can further estimate that tablets of approximately 983,000 packages were split, even though they were unscored, with 655,000 packages being split that were not allowed to be split.

There are many conceivable reasons for tablet splitting. Drugs with a narrow therapeutic range may frequently require dose adjustments. This may explain the high frequency of splitting of phenprocoumon tablets in our study population (Table 1). Another important reason for tablet splitting may be that the available doses fit poorly to the daily dose approved for a major indication (e.g. due to new post-marketing evidence), which may explain the high frequency of splitting of spironolactone tablets. About 40% of the split lisinopril tablets and over 20% of the split torasemide and metoprolol succinate tablets were divided because the patients required different doses of one drug (e.g. one tablet in the morning and half a tablet in the evening). However, Table 1 also shows that drugs for chronic use, like simvastatin or metoprolol, are frequently split although in most cases tablets with lower strengths are available. In our study population, tablets of the higher price categories were more frequently to be split than

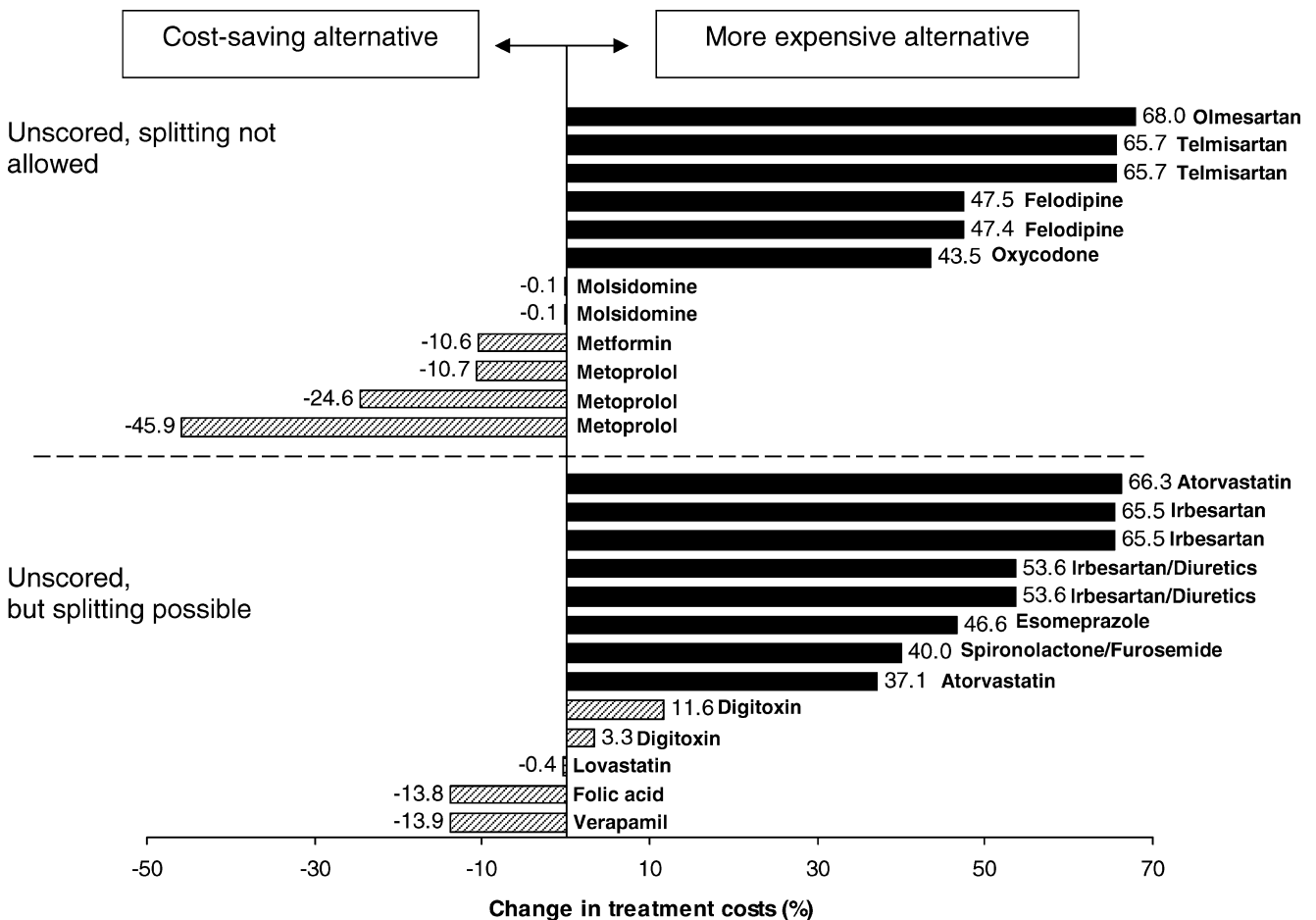


Fig. 3 Impact of switching from the actually split unscored brand to the cheapest available alternative on drug costs. Included are all unscored tablets which were split by the patients and for which alternatives were available in the German drug market ($n=25$). Solid bars indicate a

switch to an intact tablet of half the strength, hatched bars represent a switch to a scored alternative of the same strength that was suitable for splitting. Bars to the right indicate increases in treatment costs, bars to the left denote decreases in treatment costs

tablets of the lowest price categories, and patients split tablets of higher strengths twice as often. Indeed, the splitting of tablets with lower strengths is more likely

caused by medical reasons. In contrast, the splitting of a tablet with higher strength results in most cases in a dose that could also be administered as another unsplit form

Table 3 Relationship between drug characteristics and tablet splitting

	No. of split tablets (%)	No. of unsplit tablets (%)	Odds ratio (CI 95%)	Adjusted odds ratio ^a (CI 95%)
TOTAL	762 (100)	2,396 (100)		
Unit price				
<0.19€	128 (17)	683 (29)	1.0	1.0
≥0.19€≤0.34€	237 (31)	539 (22)	2.3 (1.8–3.0)	2.5 (2.0–3.2)
≥0.34€ ≤0.61€	221 (29)	548 (23)	2.2 (1.7–2.7)	2.1 (1.6–2.7)
≥0.61€	176 (23)	626 (26)	1.5 (1.2–1.9)	2.2 (1.7–3.0)
Score line ^b				
Unscored tablets	66 (9)	644 (27)	1.0	1.0
Scored tablets	696 (91)	1,574 (66)	4.3 (3.3–5.6)	4.4 (3.3–5.8)
Strength				
Lowest strength of a brand	213 (28)	1,141 (48)	1.0	1.0
Higher strength of a brand	549 (72)	1,255 (52)	2.3 (1.9–2.8)	1.8 (1.5–2.1)

^a All parameters (unit price, score line, strength) were included in the model.

^b Data on 178 packages were missing.

suggesting that other than medical reasons triggered the process. Finally, the splitting of tablets with higher strengths obviously reduces the demand of drug packages. Because in Germany patients have to effect co-payments for each purchased package, there is also an economic benefit for patients who accept the splitting of tablets.

Our results also revealed that a considerable proportion of split drugs were unscored even though for 62.5% of the drugs more suitable alternatives were available. This might be due to the lack of information in the SPC and PL making it almost impossible to consider this important detail. Moreover, when information was available it was not readily accessible and required intensive screening of the text. Only 22.5% of the analysed SPCs of the unscored split tablets contained explicit information about the divisibility and even in some SPCs of extended release formulations information on divisibility was missing. Worryingly, several brands must not be broken even though they were manufactured with score lines and so underlining the common belief that a score line is an indicator of acceptable fragmentation; they were indeed split quite often.

A first step to improve the information on divisibility in the SPCs has already been initiated by the European authorities [21] and, for all tablets with a score line, information must be given in the future whether or not reproducible dividing of the tablets has been shown. There is, however, no recommendation for unscored tablets and for tablets that are not allowed to be split. From the study of Rodenhuis [1] we know that patients sometimes split tablets on their own initiative without the knowledge of their physician. Therefore, detailed information on divisibility of all oral formulations in the PL is required to avoid medication errors. Another even more promising way to communicate information on divisibility would be to indicate this information directly on the tablet, or at least to bar manufacturers from using score lines on brands that must not be broken.

Some limitations of the study need to be mentioned. First, we did not detect splitting when patients split a tablet to facilitate swallowing, but then took all fragments of the tablet. While having little effect on the accuracy of dosing this could lead to an underestimation of the frequency of tablet splitting. Second, for 18% of the medications, detailed dosage information was missing and these compounds were thus not included in the analysis. This could lead to both an over- or underestimation of the frequency of tablet splitting. But even if we assume that all tablets were taken unsplit in the 726 cases where patients filled in an *x* instead of the exact number of tablets, the frequency of tablet splitting in the population would still be rather high (19.6% instead of 24.1%).

In conclusion, the splitting of solid galenic formulations in Germany is a frequent habit that may be driven by

medical or economic considerations. However, 7.4% of our patients are challenged to manage the splitting of formulations that are not suitable for splitting, and roughly 3% of our patients break tablets that must be taken undamaged. Therefore, physicians should only prescribe the splitting of tablets when they feel confident that the tablets are indeed suitable for splitting and when they ascertain that the patients are able to split the prescribed tablets accurately. There is thus an urgent need to improve information on divisibility in the SPC and PL to avoid medication errors. Moreover, pharmaceutical companies should abstain from producing tablets with pseudo-score lines, which may nourish a dangerous illusion in both patients and health care providers with potentially serious consequences.

Acknowledgements This study is part of a larger quality improvement project, which is supported by grant No. 217-43794-6/8 from the German Ministry of Health and Social Security. We are grateful to the participating GPs in Saxony-Anhalt who helped us to perform a questionnaire survey with a good response rate.

References

- Rodenhuis N, De Smet PAGM, Barends DM (2004) The rationale of scored tablets as dosage form. *Eur J Pharm Sci* 21:305–308
- Van Santen E, Barends DM, Frijlink HW (2002) Breaking of scored tablets: a review. *Eur J Pharm Biopharm* 53:139–145
- Cohen JS (1999) Ways to minimize adverse drug reactions. Individualized doses and common sense are key. *Postgrad Med* 106:163–172
- Wrenger E, Müller R, Moesenthin M, Welte T, Frölich JC, Neumann KH (2003) Interaction of spironolactone with ACE inhibitors or angiotensin receptor blockers: analysis of 44 cases. *BMJ* 327:147–149
- Backman JT, Kivistö KT, Olkkola KT, Neuvonen PJ (1998) The area under the plasma concentration-time curve for oral midazolam is 400-fold larger during treatment with itraconazole than with rifampicin. *Eur J Clin Pharmacol* 54:53–58
- Dalen P, Dahl ML, Ruiz ML, Nordin J, Bertilsson L (1998) 10-Hydroxylation of nortriptyline in white persons with 0, 1, 2, 3, and 13 functional CYP2D6 genes. *Clin Pharmacol Ther* 63:444–452
- Stafford RS, Radley DC (2003) The potential of pill splitting to achieve cost savings. *Am J Manag Care* 8:706–712
- Bachynsky J, Wiens C, Melnychuk K (2002) The practice of splitting tablets: cost and therapeutic aspects. *Pharmacoeconomics* 20:339–346
- Cohen CI, Cohen SI (2000) Potential cost savings from splitting newer psychotropic medications. *Psychiatr Serv* 51:517–529
- MMI Pharmindex Datenbestand Version 2005 July 15 [compact disc]. Medizinische Medien Informations GmbH, Neu-Isenburg
- Bergk V, Gasse C, Schnell R, Haefeli WE (2004) Requirements for a successful implementation of drug interaction information systems in general practice: results of a questionnaire survey in Germany. *Eur J Clin Pharmacol* 60: 595–602
- Wensing M, Broge B, Kaufmann-Kolle P, Andres E, Szecsenyi J (2004) Quality circles to improve prescribing in primary medical care: what is their actual impact? *J Eval Clin Pract* 10:457–466
- Kaltschmidt J, Gallin S, Haefeli WE (2004) Essential functional requirements for an effective electronic drug information system in a hospital. *Int J Clin Pharmacol Ther* 42:615 (abstract)

14. Cook TJ, Edwards S, Gyemah C, Shah M, Shah I, Fox T (2004) Variability on tablet fragment weights when splitting unscored cyclobenzaprine 10 mg tablets. *J Am Pharm Assoc* 44:583–586
15. Polli JE, Kim S, Martin BR (2003) Weight uniformity of split tablets required by a Veterans Affairs policy. *J Manag Care Pharm* 9:401–407
16. Atkin PA, Finnegan TP, Ogle SJ, Shenfield GM (1994) Functional ability of patients to manage medication packaging: a survey of geriatric inpatients. *Age Ageing* 23:113–116
17. Rodenhuis N, De Smet PAGM, Barends DM (2003) Patient experiences with the performance of tablet score lines needed for dosing. *Pharm World Sci* 25:173–176
18. Biron C, Licznar S, Hansel S, Schved JF (1999) Oral anticoagulant drugs: do not cut tablets in quarters. *Thromb Haemost* 82:1201
19. Fawell NG, Cookson TL, Scranton SS (1999) Relationship between tablet splitting and compliance, drug acquisition cost, and patient acceptance. *Am J Health-Syst Pharm* 56:2542–2545
20. Schwabe U (2006) Arzneiverordnungen 2004 im Überblick. In: Schwabe U, Paffrath D (eds) *Arzneiverordnungsreport 2005*. Springer, Berlin Heidelberg New York, pp 3–36
21. European Commission (2005) Notice to applicants. A guideline on summary of product characteristics. Available from: <http://pharmacos.eudra.org/F2/eudralex/vol-2/C/SPCGuidRev1-Oct2005.pdf>. Accessed: March 21, 2006