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ORIGINAL RESEARCH ARTICLE

Opportunities to Reduce Medication Regimen Complexity

A Retrospective Analysis of Patients Discharged from a University Hospital in Germany

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Abstract
Background Numerous characteristics of a medication regimen can weaken patient adherence to drug therapy and thus impair clinical outcomes of drug therapy.
Objective The aim of the study was to investigate the prevalence of medication regimen characteristics that are known to reduce patient adherence to drug therapy. Furthermore, we assessed to what extent complex medication regimens can possibly be simplified through different strategies.
Methods We retrospectively evaluated the medication regimens of 500 consecutive patients discharged from the University Hospital of Heidelberg, Germany, in whom the dosages of all drugs were specified. The medication regimens were extracted from the discharge letters issued between 1 January 2007 and 29 December 2007. Each medication regimen was checked for the presence of seven regimen characteristics that are known to reduce patient adherence, and theoretical viable strategies to avoid four of the respective characteristics were identified. The extent of possible simplification through the identified strategies was evaluated for the overall study population and the subgroup of elderly patients (≥65 years) with polypharmacy (≥5 drugs).
Results On average, every medication regimen in the overall study population had 2.9 ± 1.7 (standard deviation) characteristics (range 0–7) known to impair patient adherence. In contrast, the medication regimens of elderly patients with polypharmacy contained 3.7 ± 1.6 characteristics (range 0–7) known to impair patient adherence. The most prevalent complexity characteristics in the overall study population were prescription of ≥1 drug with multiple doses per day (441 patients), ≥3 drugs with different dosing intervals (349 patients), tablet splitting (223 patients), followed by ≥12 daily drug administrations (190 patients). Almost half of the prescribed tablet splitting could be prevented. Moreover, 17.9 % of the multi-dose prescriptions could be switched to once-daily dosing, and thus reduced the number of drugs with different dosing intervals and the number of daily drug administrations. The combined intervention reduced the total number of potentially preventable complexity characteristics by 18.3 % (from 2283 to 1865 characteristics) without reducing prescription quality.
Conclusion Almost one-fifth of all regimen complexity characteristics relevant for patient adherence were avoidable by simple modifications of the medication scheme, stressing the need for targeted interventions.

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1 Background

Patient adherence to drug treatment is a major modulator of the success of drug therapy. In clinical practice, adherence can be limited by a multitude of patient factors, including a decline in cognitive function and patients' skeptical views of the benefits of long-term treatment and its consequences on

health [1–3]. In addition to patient-specific factors, medication-related criteria have also gained importance as predictors of patient adherence, mainly for two reasons. First, with increasing life expectancy also the patients' susceptibility for age-related chronic diseases, such as arthritis, heart disease and diabetes, increases [4]. As a consequence, patients with multiple co-morbidities have a high prevalence of polypharmacy [5, 6], i.e. concurrent exposure to >4 drugs [7, 8]. Hence, drug treatment will become demanding due to the number of diseases and the respective drugs to be taken. It will also become a complex task because of the continuous evolution of the diseases requiring permanent care and adaptation of treatment. Following the idea of personalized medicine, standardized medication regimens will therefore require continuous adaptation to the current clinical situation. Hence, as complexity of drug regimens increased over the last years so did non-adherence [9, 10], while quality of life decreased [11]. Indeed, complex medication regimens (defined as ≥3 drugs with different dosing intervals and ≥1 drug with different dosages depending on the time of day) doubled the proportion of non-adherent patients [10]. The complexity of a medication regimen has been generally defined as the number of medications and daily administrations of distinct drugs [2, 12–17]. Only very few authors included further characteristics that are likely to be relevant for complexity if present in a regimen such as demanding dosage forms (e.g. inhaler, eye drops or syringes for subcutaneous injection), special directions to be followed (e.g. food-dosing restrictions) or challenging drug handling (e.g. tablet splitting) [12, 14, 16].

In addition to its detrimental impact on patient adherence, complexity of medication regimens may also promote medication errors [10, 18, 19], thus inducing adverse drug events and therapeutic failure [20–23]. Therefore, whenever possible the complexity of a medication regimen should be minimized to enable patients to adhere to their prescribed medication regimen and thus to improve health-related outcomes.

In a large set of consecutive prescriptions, we assessed the prevalence of distinct factors known to contribute to medication complexity and evaluated overall complexity of the medication regimens. We then defined potential strategies to prevent individual factors and quantified the impact of single measures for complexity reduction in these prescriptions.

2 Methods

2.1 Definition of Complexity

We conducted a literature search using MEDLINE to identify medication regimen characteristics that have been linked with medication regimen complexity and patient adherence. The following search terms (all fields including MeSH terms) were used: 'medication regimen (complexity)', '(non-)compliance', '(non-)adherence', 'polypharmacy', 'drug administration' and 'risk factors'.

The following indicators were reported to negatively correlate with patient adherence: dosing frequency [1, 9, 12, 17, 18, 24–31], food instructions [9, 12, 18], pill burden (number of pills per day) [9, 12], number of doses per day [12, 32], total number of medications [33], exact dose timing [18], use of inhaled drugs [10], tablet splitting [10, 34], ≥3 drugs with different dosing intervals [10] and drugs with different dosages at different times [10, 31].

We chose seven characteristics from all ten characteristics reportedly reducing patient adherence: (i) ≥1 drug with multiple doses per day [17]; (ii) ≥3 drugs with different dosing intervals [10]; (iii) tablet splitting [10]; (iv) ≥12 drug administrations per day [32]; (v) ≥1 drug with different dosages depending on the time of day [10]; (vi) necessity to take ≥1 drug with food [9]; and (vii) the administration of inhaled drugs [10].

It should be noted in particular that some of these characteristics relate to the individual prescription (≥1 drug with multiple doses per day, tablet splitting, ≥1 drug with different dosages depending on the time of day, necessity to take ≥1 drug with food, and the administration of inhaled drugs) while some of these characteristics relate to the whole medication regimen (≥3 drugs with different dosing intervals and ≥12 drug administrations per day).

Some indicators describe similar or closely related medication regimen characteristics leading to reduced patient adherence. In this case we chose the most comprehensive characteristic, e.g. while each characteristic '≥1 drug with multiple doses per day' [17], '3-times-daily regimens', and '4-times-daily regimens' [25] correlate with non-adherence, all of those characteristics are fully considered by the characteristic '≥1 drug with multiple doses per day' [17]. Alternatively, pill burden [9, 12], total number of medications [33] and doses per day [12, 32] were subsumed under '≥12 drug administrations per day' [32]. Because exact timing and food requirements were not specified in the electronic prescriptions, timing was not taken into account and food instructions were restricted to drugs whose pharmacodynamics make concurrent food intake mandatory (i.e. antidiabetic drugs such as short-acting insulins, glinides and sulfonylureas).

2.2 Assessment of Complexity in Electronic Prescriptions

After approval by the responsible Ethics Committee of the Medical Faculty of Heidelberg we retrospectively evaluated medication regimens of 500 discharge letters issued between 1 January 2007 and 29 December 2007 within the

Table 1 Medication regimen characteristics known to modulate patient adherence and strategies for their prevention

Medication regimen characteristic	Possible strategy to avoid this characteristic	Limitations of the simplification strategy
Tablet splitting	Substitution by a drug with lower strength	No simplification when the regimen consisted of different single doses (e.g. 10 mg in the morning and 5 mg at noon) because simplification would then imply that several drugs with different strengths are prescribed and thus pill burden will increase. Tablets were considered as 'not suitable' for splitting if they were unscored and considered as 'not allowed' to split if they were unscored and not allowed to split according to information from the marketing authorization holder
≥1 drug with multiple doses per day	Adjustment of the prescribed dosing frequency to the approved dosing frequency or switch to long-acting drugs (e.g. switch to extended-release dosage forms) for as many drugs as possible	Recommended dosing frequencies referred to information in the summary of product characteristics. A switch to once-daily-administered long-acting drugs was performed if the dose of the long-acting drug was within the bioequivalence range of 80–125 % of the originally prescribed daily dose. No switch was performed if use of tablet splitting or, for example, more than one tablet was necessary to meet the prescribed dose. Different salts of the active component were considered to be equal
≥3 drugs with different dosing intervals	Adaptation of dosing intervals by switching to long-acting drugs	
≥12 drug administrations per day	Substitution by a fixed-dose combination and reduction of administrations by switching to long-acting drugs	No switch to a combination drug product if tablet splitting was necessary to achieve the prescribed dose
≥1 drug with different dosages depending on time of day	Because of the therapeutic and physiological necessity of dose individualization (e.g. short-acting insulin, phenprocoumon) and the goal of minimization of pill burden, simplification was not attempted in this assessment	
Necessity to take ≥1 drug with food	Not possible	Because immediately after administration food intake is required for short-acting insulins, sulfonylureas, or glinides, there is no simplification strategy available
Application of inhaled drugs	Because the treatment guidelines for asthma and COPD generally recommended the use of inhaled drugs as first-line therapy, a change of the regimen to oral treatment was considered inappropriate and therefore this characteristic was not applied	

COPD chronic obstructive pulmonary disease

electronic prescribing system (AiD*Klinik*®) of the University Hospital of Heidelberg, Germany. Included were consecutive letters of five internal medicine wards (100/ward) that contained a defined dosage regimen (also including 54 prescriptions dosed according to international normalized ratio (INR)) assuming to obtain a representative profile. Each medication regimen was evaluated for the prevalence of the seven characteristics as a measure of complexity. For this purpose, each discharge letter was reviewed by a pharmacist who rated how many characteristics applied to the respective medication regimen. With the help of a second clinical pharmacist, interrater agreement as a quality measure was assessed on the basis of a random sample of 5 % of the discharge letters. For each prevalent characteristic, an arbitrary score of one was allocated. The sum of all applicable characteristics was defined as medication regimen complexity.

In the discharge letters, dosing instructions were specified according to a morning–noon–evening–night schedule or as variable dosing instructions such as 'according to INR' or 'according to blood glucose'. Dosing instructions such as 1-1-0-0 and 1-0-1-0 were rated as different dosing intervals, even though the number of doses per day was identical. Tablet splitting was considered present if the physician prescribed a fraction of the tablet (e.g. half) or if the prescribed dose could only be achieved by tablet splitting. When vitamin K antagonists (phenprocoumon and warfarin) were prescribed 'according to INR' we assumed that tablet splitting was inevitable because in Germany, and also in this group, almost all patients are on long-acting phenprocoumon. To assess the worst-case scenario, drugs with dosing intervals >24 hours were included in the number of drug administrations per day, even though the patient did not take the drug every day.

Table 2 Demographics, discharge departments and medication use of overall study population and elderly subgroup with polypharmacy

	Overall study population	Subgroup of elderly patients with polypharmacy
No. of patients	500	151
Mean age [y (range)]	55.4 (17–89)	71.8 (65–89)
Sex [n (%)]		
Female	220 (44.0)	59 (39.1)
Male	280 (56.0)	92 (60.9)
Discharge from department (no. of patients)		
Endocrinology and metabolism	100	37
Psychosomatic and general internal medicine	100	23
Cardiology, angiology and pneumology	100	45
Gastroenterology, infectious diseases, intoxication	100	29
Haematology, oncology and rheumatology	100	17
Mean no. of prescribed drugs (range)	7.2 (1–20)	9.0 (5–20)
Top five prescribed drug classes [ATC code] (%)	A02: Drugs for acid related disorders (9.0)	B01: Antithrombotic agents (13.6)
	B01: Antithrombotic agents (8.0)	C03: Diuretics (11.3)
	C03: Diuretics (7.0)	C09: Agents acting on the renin-angiotensin system (10.9)
	J01: Antibacterials for systemic use (7)	A02: Drugs for acid related disorders (9.7)
	C09: Agents acting on the renin-angiotensin system (6.0)	C07: Beta blocking agents (9.6)

ATC Anatomical Therapeutic Chemical

Different dosages depending on the time of day were applicable if the patient was prescribed different dosages in the morning, at noon, in the evening or at night, or if special instructions such as 'according to INR' (phenprocoumon or warfarin) or 'according to blood glucose' (insulin) were given. We classified prescribed drugs as either long-term ($\geq$3 months' administration) or short-term ($<$3 months' application) medication. The distinction was made by analysing physicians' notes corresponding to individual prescriptions. Medication with the instruction 'to be taken as needed' was also defined as short-term medication, as was medication with dosing instructions such as 'to be taken until INR $>$2'.

2.3 Impact of Strategies to Reduce Medication Regimen Complexity

To reduce medication regimen complexity we identified possible strategies to avoid triggering medication regimen characteristics (see Table 1). Our intervention addressed a defined fraction of complexity characteristics and, for these characteristics, assessed theoretical and actual options for their prevention. If only theoretical options were available and suitable options for modification in daily practice were currently absent, we categorized them as 'potentially preventable'. As an example, thrice-daily administration of captopril could be avoided by applying an extended-release formulation but there is no such formulation available. If, for a complexity issue, a practical specific solution was also available, we categorized it as 'immediately preventable'. All stated preventive strategies are theoretical considerations and do not include active clinical decisions. Our retrospective study thus aimed to identify promising simplification strategies and to assess the extent to which they could help reduce medication regimen complexity.

Every simplification strategy (e.g. avoiding of tablet splitting and multiple dosing per day) was first evaluated on the basis of individual prescriptions. Then the dimension of possible simplification was evaluated at patient level (proportion of completely, partially and not preventable complexity characteristics) and expressed as a reduction of mean complexity score.

2.4 Statistical Analysis

All data were analysed descriptively and reported as proportions and means including standard deviation (SD). Medication regimens before and after adoption of

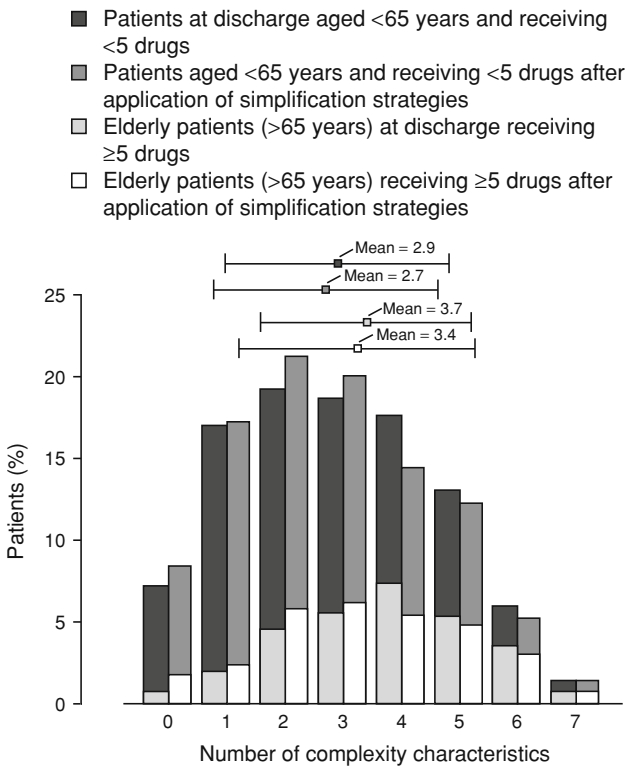


Fig. 1 Proportion of complexity characteristics in a population of 500 consecutive patients discharged from a university hospital before and after application of possible simplification strategies

simplification strategies were compared by McNemar's test for all nominal variables and Wilcoxon matched-pairs signed-rank test for metric data. Comparisons between different study populations were performed by unpaired t-test. Statistical significance was accepted for $p < 0.05$. All analyses were conducted with SPSS version 19 (IBM® SPSS® Statistics, Ehningen, Germany).

3 Results

We retrospectively evaluated medication regimens of 500 consecutive discharge letters that were issued on five internal wards (100 from each ward) referring to 280 male and 220 female patients (44 %; Table 2). With the help of a second clinical pharmacist, interrater agreement as a quality measure was assessed. Rating criteria were unambiguously specific and, hence, the κ coefficient was 1. The complexity score of the evaluated medication regimens ranged from 0 to 7 (maximum possible) with a mean value of 2.9 (SD ± 1.7; Fig. 1) in the overall study population. The medication regimen of 464 patients (93 %) contained at least one complexity characteristic. The most prevalent characteristic was the prescription of ≥1 drug with multiple doses per day, which occurred in 441 patients (88.2 %). The least frequent characteristic was the use of inhaled drugs, which occurred in only 39 patients (7.8 %; Fig. 2a). In only 5 of 189 patients, the complexity characteristic '≥12 administrations per day' was attributed because drugs with a dosage interval >24 hours were also included in the number of drug administrations per day (as defined in Sect. 2), even though the patient presumably did not take the drug every day. The total number of individual complexity characteristics present in the 500 medication regimens was 2649, with 2283 of them being potentially preventable.

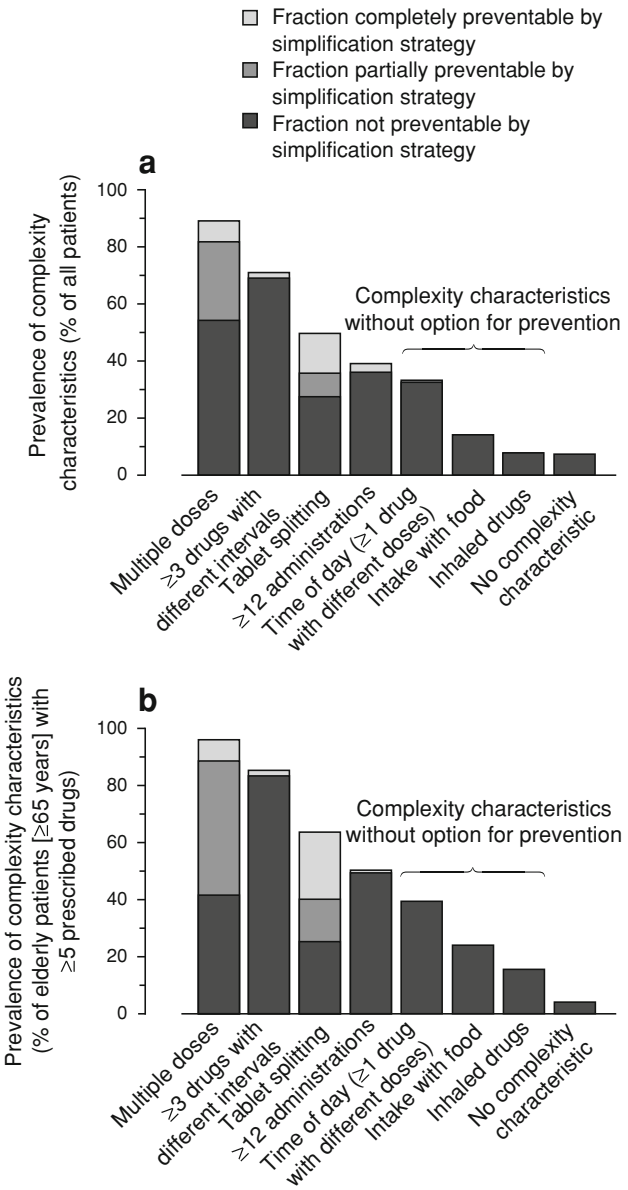


Fig. 2 (**a**) Prevalence of complexity characteristics in 500 internal medicine patients discharged from a university hospital. If a characteristic was present more than once in a patient, it was only considered once. (**b**) Prevalence of complexity characteristics in 151 elderly patients (≥65 years) with polypharmacy (≥5 prescribed drugs) discharged from a university hospital. If a characteristic was present more than once in a patient, it was only considered once

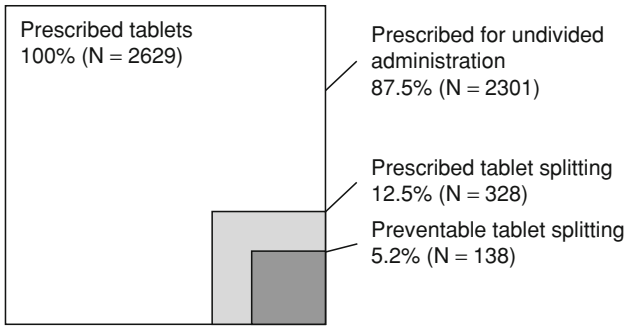


Fig. 3 Options to prevent tablet splitting in the medication of 500 patients discharged from a university hospital

3.1 Subgroup of Elderly Patients with Polypharmacy

Because elderly patients (defined as ≥65 years [7]) with multiple co-morbidities and polypharmacy (defined as ≥5 prescribed drugs) [7, 8] will likely benefit in particular from such an optimization strategy, we evaluated this subgroup separately. The inclusion criteria were fulfilled by 151 (30.2 %) of 500 patients, referring to 92 male and 59 female patients (Table 2). Their complexity scores ranged from 0 to 7. The mean value of 3.7 (SD ± 1.6; Fig. 1) was significantly higher in this subgroup than in the remaining study population (2.6 ± 1.7; $p < 0.001$). The medication regimen of 147 elderly patients with polypharmacy (97.4 %) contained at least one complexity characteristic. The most prevalent characteristic was the prescription of ≥1 drug with multiple daily doses, which occurred in 144 patients (95.4 %; Fig. 2b). The least frequent characteristic was the use of inhaled drugs, which occurred in only 23 patients (15.2 %). In only one of 75 patients, the complexity characteristic '≥12 administrations per day' was attributed because drugs with a dosage interval >24 hours were also included in the number of drug administrations per day (as defined in the Methods section), even though this patient presumably did not take the drug every day. The total number of individual complexity characteristics present in the 151 medication regimens was 1119, with 789 (70.5 %) of them being potentially preventable.

3.2 Substitution by Drugs with Lower Strength to Reduce Tablet Splitting (Overall Study Population)

Of 3556 prescribed drugs, 2629 (74 %) were tablets and 328 of these tablets (12.5 %) had a dosing schedule that included tablet splitting (Fig. 3). In almost half of these prescriptions (42.1 %) a switch to a drug with lower strength was possible, thus avoiding tablet splitting ($p < 0.001$). Of the remaining 190 (57.9 %) drugs that could not be switched to a drug with lower strength in 86 (45.3 %) prescriptions, the switch was not possible because of the lack of a dosage form with lower strength, and in 104 (54.7 %) the switch was not possible because of variable dosing (e.g. according to INR or different dosing in the morning and evening). In the latter case, a switch to two or more drugs with lower strength would have increased pill burden and thus potentially decrease patient adherence. Substitution by drugs with lower strength completely avoided tablet splitting in 69 (30.9 %) of 223 patients ($p < 0.001$; Fig. 2a). Thereby, the mean complexity score decreased from 2.9 (±1.7) to 2.8 (±1.7; $p < 0.001$). In 41 patients (18.4 %), the number of split drugs could be reduced, whereas in approximately half of the patients (113; 50.7 %) the intervention had no influence on frequency and extent of tablet splitting (Fig. 2a).

3.3 Subgroup of Elderly Patients with Polypharmacy

Of 1366 prescribed drugs, 1032 (75.5 %) were tablets and 158 (15.3 %) had a dosing schedule that included tablet splitting. In almost half of these prescriptions (47.5 %) a switch to a drug with lower strength was possible, thus avoiding tablet splitting ($p < 0.001$).

Of the remaining 83 (52.5 %) drugs that could not be switched to a drug with lower strength, in 39 (47.0 %) prescriptions the switch was impossible because of the lack of a dosage form with lower strength, and in 44 (53.0 %) the switch was impossible because of variable dosing (e.g. according to INR or different dosing in the morning and evening). In the latter case, a switch to two or more drugs with lower strength would have increased pill burden and thus potentially decreased patient adherence. Substitution by drugs with lower strength completely avoided tablet splitting in 35 (35.8 %) of 95 patients ($p < 0.001$; Fig. 2b). Thereby, the complexity score decreased from 3.7 (±1.6) to 3.5 (±1.7; $p < 0.001$). In 22 patients (23.2 %) the number of split drugs could be reduced, whereas in 39 patients (41.1%) the intervention had no influence on frequency and extent of tablet splitting (Fig. 2b).

3.4 Frequency and Prevention of Inappropriate Tablet Splitting (Overall Study Population)

Moreover, we examined frequency and options for prevention of inappropriate tablet splitting. Of all prescribed split tablets, 24 (7.3 %) were unscored and thus not suitable for splitting. In our study, 1.5 % of all split tablets were not allowed to be split. Approximately one-third (7/24) of the tablets that were not suitable for splitting could not be substituted with tablets of appropriate strength, and for another third (8/24), tablets with appropriate strength were available. In the remaining nine tablet

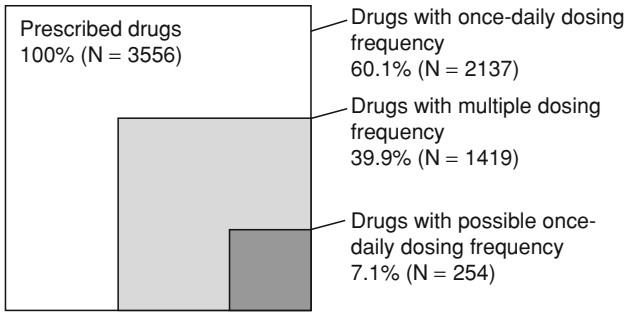


Fig. 4 Options to switch to once-daily dosing frequency in the medication of 500 patients discharged from a university hospital

prescriptions, inappropriate splitting could have been prevented with measures beyond our specified guidelines (e.g. by substitution with two drugs of different strength to match prescriptions such as 1-0-1/2-0).

3.5 Impact of Adjustment of the Prescribed Dosing Frequency (Overall Study Population)

As shown in Fig. 4, of 3556 prescribed drugs, 1419 (39.9 %) were drugs with multiple doses per day. In 17.8 % of these drugs the switch to once-daily dosing frequency was possible ($p < 0.001$), thus completely preventing multiple doses in 36 (8.2 %) of 441 patients ($p < 0.001$) and partially preventing multiple doses in 138 (31.3 %) of 441 patients (Fig. 2a). Of these drugs, in 235 (92.5 %) the drug label (Summary of Product Characteristics [SPC]) recommended once-daily dosing and these drugs might therefore be switched accordingly. Another 13 (5.1 %) drugs could be switched to extended-release dosage forms and 6 (2.4 %) to higher dose, instant-release formulations. Thereby, 12 or more daily drug administrations could be avoided in 14 of 190 (7.4 %) patients ($p < 0.001$), and in 10 (2.9 %) of 349 patients at least three drugs with different dosing intervals could be prevented ($p = 0.002$) [Fig. 2a]. Concurrently, in 1 (0.5 %) of 219 patients this switch could also have prevented tablet splitting, and in 1 (0.6 %) of 159 the use of different dosages depending on time of day was prevented.

3.6 Subgroup of Elderly Patients with Polypharmacy

Of 1366 prescribed drugs in this subgroup, 484 (35.4 %) were drugs with multiple doses per day. In 118 (24.4 %) of these drugs the switch to once-daily dosing frequency was possible ($p < 0.001$), thus completely preventing multiple doses in 11 (7.6 %) of 144 patients ($p = 0.001$) and partially preventing multiple doses in 71 (47.0 %) of 144 patients (Fig. 2b). In 108 (91.5 %) of these drugs the drug label (SPC) recommended once-daily dosing and these drugs might therefore be switched accordingly. Another 10 (8.5 %) drugs could be switched to extended-release dosage forms. Thereby, 12 or more daily drug administrations could be avoided in 1 of 75 (0.7 %) patients, and in 3 (2.0 %) of 128 patients at least three drugs with different dosing intervals could be prevented (Fig. 2b).

3.7 Substitution by a Fixed-Dose Combination (Overall Study Population)

In only 9 of the 500 (1.8 %) evaluated medication regimens could we substitute two drugs by a fixed-dose combination, and in two cases (0.4 %) two identical drugs were prescribed with different dosages that could be switched to a drug product of the required strength. Thereby, in one patient the number of daily drug administrations decreased below 12. In seven further cases (0.8 %), a fixed-dose combination with the required single dose existed but the daily doses of the single drugs varied in a way that prevented switching.

3.8 Subgroup of Elderly Patients with Polypharmacy

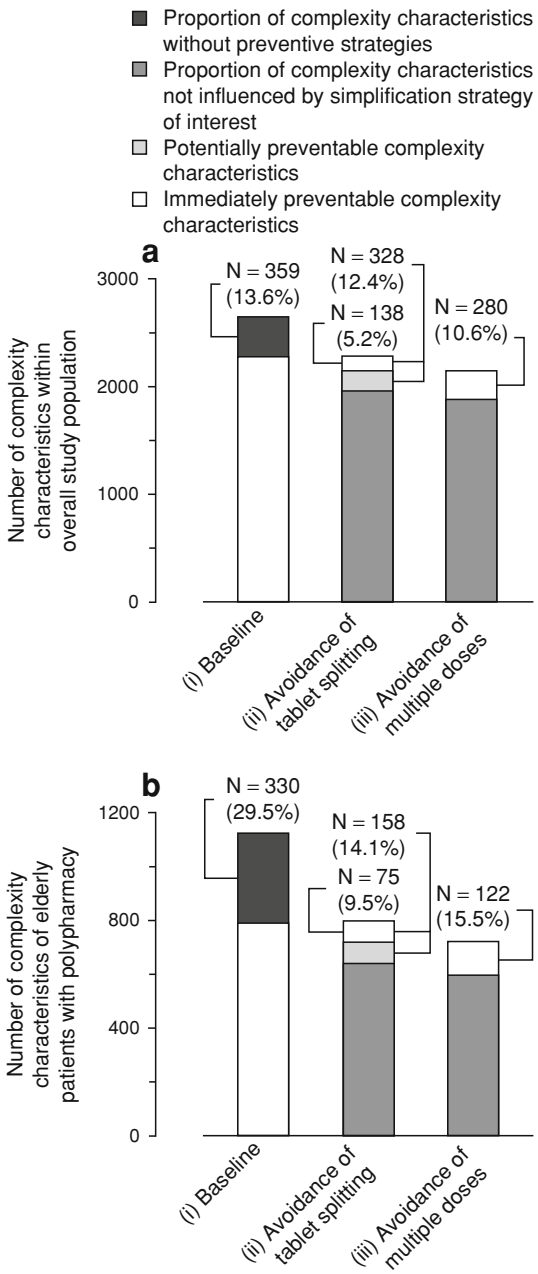
In only 4 of the 151 (2.6 %) evaluated medication regimens could we substitute a drug pair by a fixed-dose combination. This intervention did not reduce the number of daily administrations below 12 in any of these patients.

3.9 Effect of Reducing Tablet Splitting, Adjustment of Dosing Frequency and Using Fixed-Dose Combinations on the Complexity Characteristics and Score (Overall Study Population)

The combined strategy of avoiding tablet splitting and multiple doses while promoting fixed-dose combinations reduced the complexity score from 2.9 (±1.7) to 2.7 (±1.8; $p < 0.001$; Fig. 1) by eliminating almost one-fifth (418 of 2283; 18.3 %) of the complexity characteristics by the selected three prevention strategies (Fig. 5a). The most effective strategy to reduce complexity was the prevention of tablet splitting. Of the 3556 prescribed drugs, 385 (10.8 %) were used as short-term treatment. Only 2 of the 418 potentially solved complexity characteristics refer to short-term medication. Thus, the findings emphasize the relevance of our simplification strategies to enhance patients' adherence to long-term self-administered medications and stress their appropriateness for this purpose.

3.10 Subgroup of Elderly Patients with Polypharmacy

The combined strategy of avoiding tablet splitting and multiple doses while promoting fixed-dose combinations reduced the complexity score from 3.7 (±1.6) to 3.4 (±1.8; $p < 0.001$; Fig. 1) by eliminating almost one-quarter (196



◀ **Fig. 5** (**a**) Cumulative reduction of complexity characteristics of overall study population by a theoretical application of different prevention strategies. (i) Total number of complexity characteristics that were found in 500 consecutive discharge letters containing prescriptions of 3556 drugs and proportion of complexity characteristics without preventive strategies (*black area*); (ii) Targeted complexity characteristics that could be prevented by avoiding tablet splitting (*white area*) as a proportion of the total number of prescriptions with tablet splitting (*aggregation of white and light grey area*); (iii) Complexity characteristics that could be reduced by avoiding multiple doses (*white area*). (**b**) Cumulative reduction of complexity characteristics of elderly patients with polypharmacy by a theoretical application of different preventive strategies. (i) Total number of complexity characteristics that were found in 500 consecutive discharge letters containing prescriptions of 3556 drugs and proportion of complexity characteristics without preventive strategies (*black area*); (ii) Targeted complexity characteristics that could be prevented by avoiding tablet splitting (*white area*) as a proportion of the total number of prescriptions with tablet splitting (*aggregation of white and light grey area*); (iii) Complexity characteristics that could be reduced by avoiding multiple doses (*white area*)

of 789; 24.8 %) of the complexity characteristics by the selected three prevention strategies (Fig. 5b). The most effective strategy to reduce complexity was the prevention of tablet splitting.

4 Discussion

Non-adherence is one of the most relevant modulators of therapeutic success and is largely responsible for the gap between expected efficacy and observed effectiveness of current therapies. Potentially serious consequences of therapeutic failure include increased morbidity, mortality and hospitalization [35]. Therefore, promising interventions are necessary to enhance patient adherence and thereby improve drug safety. Furthermore, it is well known that more complex treatment regimens are also less likely followed and therefore a thorough assessment of the prevalence of complexity characteristics, especially options for their prevention, are required. Special therapies that require changing doses (e.g. anticoagulant therapy or antidiabetic therapy) are relevant causes for preventable adverse events [21] and thus simplification of medication regimens seems to be a promising approach to avoid medication errors and facilitate patient adherence. In this study, almost one-fifth of relevant complexity characteristics were potentially avoidable by simple modifications of the medication scheme and thus unnecessarily jeopardized patient adherence.

In addition to the impact on drug handling and thus the patients' readiness and possibilities to follow instructions (adherence), complexity may also adversely affect the safety of a dosing regimen. The most successful strategy to reduce complexity in our population was the prevention of tablet splitting. From all areas addressed in this study, this is also the area from which most risks may arise. Similar to an earlier study [36], in this study of hospitalized patients discharged, 12.5 % of all prescribed tablets were also split, which is roughly half the splitting rate of ambulatory patients [37, 38]. Besides decreasing patient adherence [10, 34], tablet splitting might be associated with substantial risks for safe drug application because it may modify release characteristics (slow release) or protective coating (gastric protection) through destruction of relevant coating, which currently occurs in almost 1 % of all solid oral dosage forms [37]. In this population, 7.3 % of all split tablets were unscored and 1.5 % of all split tablets must not

be split. These findings correspond well with our earlier findings in ambulatory patients [37]. On the other hand, patients are often not willing or capable of splitting tablets. Indeed, more than 70 % of elderly inpatients were not able to split tablets (mean age 81.2 years) [39]. Furthermore, over 40 % of the tablet fragments deviated by more than 10 % from the ideal weight [40], thus rendering reliable exposure difficult. Prevention of tablet splitting will therefore likely eliminate dose inaccuracies [40–43], stability problems of fragments [44] and loss by splitting [45], and thus assure more reliable dosing.

On the other hand, because the price per milligram active ingredient is often less in higher strength tablets, tablet splitting may save direct medication cost [46]. The proportion of patients who are willing to pay more for tablets with lower strength varies. While one study showed that even three-quarters of patients are willing to pay more for the medication to avoid splitting [40], another study found that more than 90 % of patients would split tablets if they were paying full price for their medication [47]. In agreement with our previous study in ambulatory patients, it was possible to avoid tablet splitting in more than half of the prescriptions and there is good evidence for improved adherence without tablet splitting [10, 36].

Another important aspect of regimen complexity is daily-dose frequency. In numerous studies it was easier to adhere to once-daily dosing regimens than to regimens with more frequent dosing [1, 24–27, 48, 49]. Indeed, in our study we were able to theoretically switch 252 (17.7 %) of 1419 prescribed drugs to a once-daily dosing frequency. Whether it is indeed essential to reduce dosing frequency as often as possible to once daily or whether it would already substantially simplify dosing regimens if thrice-daily and four-times-daily regimens were eliminated is not known. Because in several studies adherence to once-daily and twice-daily dosing frequency was similar [1, 28] it appears already beneficial if either of them is achieved. Therefore, future complexity scores should probably aim at reducing the total number of individual doses as much as possible. In recent years, new drugs with a longer half-life and thus with less frequent dosing have been approved (e.g. indacaterol as an ultra-long-acting β_2-adrenoceptor agonist), further supporting simplification of dosing regimens. Indeed, in five of eight of our patients receiving long-acting β_2-adrenoceptor agonists, a switch to once-daily indacaterol would have been possible. In different populations adherence improved after switching from free-drug regimens to fixed-dose combinations [50, 51], and effectiveness improved with the prescription of fixed-dose combinations [51]. However, this option of substitution of drug pairs with a fixed-dose combination played only a minor role in our patients.

Hence, our study showed that medication complexity can be reduced by rather simple measures. However, to do so in a large drug market such as the German market appropriate technical support will be required at the time of prescribing because it is unlikely that this task can be efficiently fulfilled without it. Obviously, we do not know yet whether a 0.2 reduction in a complexity score will indeed result in clinical improvement or enhanced medication adherence. The reduction of 0.2 score points implies that one characteristic in five patients was eliminated. In earlier studies it was shown that the proportion of non-adherent patients doubled in the presence of one complexity characteristic (e.g. use of drugs with different doses at different times) [10]. Hence, we do believe that the large number of prevalent complexity characteristics and their reduction by simple strategies suggests that patients might benefit from such low-level interventions.

5 Limitations

This study has several limitations. (i) As done by others [14, 16], we considered complexity markers as additive, which appears likely albeit not clearly proven. In agreement with some [52] but not all previous studies [14, 16], all complexity markers were assigned identical weights. This is certainly a simplification that may be resolved in a study also assessing clinical endpoints and which may bias the potential benefits estimated in this study. (ii) The retrospective nature of our study did not allow assessment of the actual improvement by reducing the complexity as perceived by the individual patient. Now that the feasibility of the approach has been shown, related endpoints may be addressed prospectively. (iii) Another important point is that our theoretical approach cannot account for well-considered, deliberate, active decisions such as dosing more frequently than once-daily in individual patients (e.g. due to adverse effects). (iv) Beyond the scope of this assessment was also consideration of circadian variability of the limited number of drugs that require a specific time of administration [53]. Furthermore, (v) we did not attempt to reduce the number of drugs to be taken with food because we only included drugs with a pharmacodynamic necessity for concurrent food intake (short-acting insulin, glinides and sulfonylureas), whereas drugs whose absorption is modified by food or fasting were not included. Thus, we likely underestimated both the impact of aligning drug and food intake on complexity and also potential options for its avoidance. (vi) We assumed that pill splitting was inevitable for vitamin K antagonists because only few dosing strengths are available in Germany and because half-strength phenprocoumon is rarely prescribed. Hence, in contrast to other countries such as the US with a

multitude of warfarin strengths, inevitable tablet splitting is likely to be the rule rather than the exception in a German patient population. Indeed, in only one patient warfarin was prescribed as opposed to 51 patients receiving phenprocoumon in our study population. Hence, we believe that we do not overestimate the need for tablet splitting of vitamin K antagonists to a relevant extent. (vii) The option of switching to a therapeutic equivalent instead of a generic substitution could further reduce the application of multiple daily dosing and thus lead to a reduction in the number of daily drug administrations and the number of different dosing intervals. Likewise, this study assessed the medication complexity in patients discharged to an outpatient setting. Assessment and required modifications might differ in inpatients or patients not administering their drugs themselves as it may differ depending on co-morbidity such as visual and mental function and, ultimately, dexterity also. (viii) Finally, we neither evaluated whether all required drugs were indeed given (underuse) nor whether potentially inappropriate medications were prescribed. Hence, the true complexity if optimum treatment would have been provided might differ from what we observed.

6 Conclusion

With few simple measures we could significantly reduce the complexity of medication regimens. Some of these characteristics have already been successfully targeted by electronic interventions [36], suggesting that the use of such tools may help reduce regimen complexity in daily practice. Evaluated prospectively, this approach will now have to prove its clinical benefits on patient satisfaction and ultimately adherence and effectiveness.

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