Eur J Clin Pharmacol (2013) 69:573–580
DOI 10.1007/s00228-012-1342-2

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Medication complexity, prescription behaviour and patient adherence at the interface between ambulatory and stationary medical care

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Received: 31 January 2012 / Accepted: 21 June 2012 / Published online: 25 July 2012

Abstract
Purpose A hospital stay is often accompanied by changes in medication therapy. The purpose of this study was to investigate the impact of a transfer across the interfaces on the complexity of therapeutic regimens and patient adherence as well as the attitudes of patients and general practitioners (GPs) towards pharmacotherapies.
Methods This was a prospective observational study that analysed the complexity of medication therapies and the adherence and attitudes of internal medicine and urology patients towards their medication(s) at three time points (hospital admission, discharge and 6 weeks after discharge). GPs of the patients recruited to the study were questioned about the follow-up medication therapy and their opinion on the medication prescribed in hospital.
Results At the time of hospital admission, 60.2 % of the study population were nonadherent. During hospitalization, the number decreased to 37.6 %, but increased to 61.2 % 6 weeks after discharge. Changes in the overall complexity of the therapy regimens were marginal and not statistically significant. Of the long-term medication regimens, 48.6 % were modified during hospital stay. The patients preferred regimens with a minimum of drug administrations. GPs stated to be willing to continue hospital prescriptions but were restricted by financial budgets.
Conclusion The results of this study confirm that an increase in adherence during a hospital stay is only transient, underlining the need for interventions to ameliorate medication adherence. They also suggest that patients prefer simple regimens. Although GPs are willing to consider their patient's preferences on pharmacotherapy, they state limitations due to financial budgets. Further studies are needed that investigate the extent to which medication therapies can be simplified and the effect of simplification on adherence.

Keywords Adherence · Complexity · Continuity of patient care · Hospitalization · Ambulatory–stationary interface

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Introduction

Insufficient adherence is a worldwide problem that is associated with increasing healthcare costs due to a worsening disease state, increased hospital admissions and death [1–3]. In developed countries, the average adherence rate to the prescribed therapy has been estimated to be only 50 % [4]. Thus, in addition to the severity of the disease, adverse drug events and treatment costs, both medication complexity and the patient's attitude towards his therapy are factors that contribute to insufficient adherence [4–7]. Also a hospital stay influences patient adherence. In Germany, the healthcare system is characterized by a rather strict separation of the ambulatory and the hospital sector, resulting in considerable discontinuity in medical care, including pharmacotherapy. It has been reported that on-going medication is modified at hospital admission for 83 % of patients [8, 9] and at discharge for 72 % [3]. Modifications in medication after the return of the patient to ambulatory care have often

been attributed to economic reasons [10] or a lack of information on the discharge medication [11, 12]. These alterations can cause drug-related problems and decrease patient adherence. An increase in medication complexity [13–16] may confuse patients due to changes in the names and appearances of the drugs [8, 17], and the trust between patient and physician may suffer owing to frequent modifications in medication [9, 18]. Finally, polypharmacy and poor adherence may result as complications of a hospital stay [1, 19]. However, despite all these factors, adherence to drug therapy is essential for the successful treatment of diseases.

Little is currently known about the magnitude and complexities of changes in medication and the concomitant changes in adherence at the interfaces between hospital and ambulatory care in Germany. Also, data on patients' attitudes towards their pharmacotherapy and on the reasons for general practitioners (GPs) to either accept or modify hospital discharge prescriptions are scarce. These aspects are the focus of the study presented here.

Methods

Study design

This prospective observational panel study focused on the medications and adherence of patients crossing the interfaces between ambulatory and hospital care under field conditions and without intervention. It was conducted at the internal medicine and urology wards of the Medical Center Hamburg–Eppendorf, a tertiary care university hospital in Germany. Participants who met legal requirements to participate in such a study (age of >18 years, written informed consent given) and who received medications to treat chronic cardiovascular and/or metabolic diseases were enrolled consecutively between March 2010 and August 2010. Patients with reduced cognitive performance or dis-/inability to communicate in the German language were excluded. The study was reviewed and approved by the Ethical Review Committee Hamburg.

Data collection and measures

Clinical and demographic aspects and the medication history of each patient were extracted from the hospital files at time of admission to the study (t0). Socio-demographic data and patients' attitudes towards medication therapy were obtained from questionnaires handed out and completed by each patients in the hospital. Based on patients' self-reporting, medication adherence was measured at admission (t0: outpatient care *before* hospital stay), at discharge (t1: inpatient care) and at 42±7 days post-discharge (t2: outpatient care *after* hospital stay) using the German version of the Medication Adherence Rating Scale (MARS-D) [18, 19]. The MARS-D consists of five items describing non-adherent behaviour. Each item is scored on a scale of 1 (= "always") to 5 (= "never") points, leading to a sum score ranging between 5 and 25 points. The higher the score, the better is the indicated medication adherence. Adherence and nonadherence were dichotomized with a cut-off point at 25 (patients with a sum score of 25 were regarded as adherent, patients with a sum score of <25 as nonadherent), as chosen in a previous study [20]. Additionally, each item of the MARS-D was dichotomized separately (score of 5=adherent; <5=nonadherent).

Discharge medication was recorded from the discharge letters at t1. At t2, a questionnaire was sent to the patients asking about their current medication and to their GP, asking about the patient's current medication. The complexity of the therapeutic regimens was analysed using the previously validated German version of the Medication Regimen Complexity Index (MRCI-D [21, 22]) for each patient at all three time points. The index consists of three sections (A, B, C) and incorporates the total number of medications to be taken, the dosage forms, dosage frequency and additional directions pertaining to the administration of the medication (s). According to strictly defined rules, each section yields a score for the respective component of complexity. These scores are ultimately summed up to express the MRCI as a single number. In line with other studies, including the original validation of the English MRCI, no cut-off values were defined in our study [22–24]. Drugs for short-term use, such as antibiotics or analgesics, were not included in the analysis. In cases of discrepancies between the medication lists returned from the patients and those returned from their GP at t2, the information from the GP was considered to be correct and used for the analysis of complexity.

In the questionnaire sent to the GPs at t2, the GPs were asked about the medication recommendations in the discharge letter, their reasons for accepting or modifying the discharge medication and their attitude towards the complexity of therapeutic regimens in general.

Data analysis

The first step consisted of analysing the overall adherence, regimen complexity and the number of prescriptions at t0, t1 and t2 using descriptive statistics. Additionally, each of the five items of the MARS-D was analysed separately. Means and standard deviations (SD) were calculated for continuous outcomes (regimen complexity, number of prescriptions and adherence) and frequencies were assessed for dichotomous outcomes (i.e. single MARS-D items). In a second step, univariate analyses of variance with repeated measures were conducted for each outcome using time as a factor (admission, discharge, follow-up) and the specific outcome as the

dependent variable. Results with a type I error rate of $p<0.05$ were considered to be statistically significant.

Patients' attitudes towards their medication as well as GPs' attitudes towards prescriptions were analysed using absolute and percentage frequencies. The relationship between categorical variables (gender, education, employment-status) and nonadherence was evaluated using the χ^2- test. The *t* test was used to assess differences between adherent and nonadherent patients in terms of age.

All analyses were performed using SPSS ver. 18.0 (IBM Corp., Armonk, NY).

Results

A total of 108 patients were enrolled in the study. Loss during follow-up was due to death ($n=2$), withdrawal of consent ($n=3$) or transfer to wards not included in the study ($n=1$). Baseline characteristics of the study population are summarized in Table 1. The mean age of the patients was 63.1 ± 12.0 years (range 26–84 years) and 83.3 % of the patients were male. The low percentage of female patients partly results from the inclusion of a urology ward, where most elective admissions are usually male. At the time of enrolment the mean number of diagnoses of chronic diseases per patient was 7.2 ± 5.3. Their mean length of hospital stay was 6.0 ± 4.4 days.

Nonadherence rates are shown in Fig. 1. The number of patients included in the analysis at t0, t1 and t2 were 88, 85 and 67, respectively. The mean MARS-D score at t0 was 23.57 ± 2.53, with 60.2 % of the patients classified as nonadherent (score<25). In the hospital (t1), the mean score increased to an average of 24.02 ± 2.07, with 37.6 % of nonadherent patients. Six weeks post-discharge (t2), the mean MARS-D score decreased to 23.91 ± 1.30), with 61.2 % of nonadherent patients ($F=1.74$, $df=1$, $p=0.193$). Although the adherence rates showed a strong tendency to vary substantially across measurement points, they did not reach strict statistical significance (Friedman test: $\chi^2=5.57$, $df=2$, $p=0.062$). The first statement of the MARS-D ("I forget to take my medication") was the item with the highest nonadherence rate (t0 = 47.7 %, t2 = 49.3 %) and the greatest deviation during hospitalization (t1), although during hospitalization the nonadherence rate with respect to this question decreased significantly to 27.1 %. Dosages were altered by fewer patients when they were in the hospital than after they were discharged. The number of patients who consciously decided "I stop taking my medicine for a while", "I decide to miss out a dose of my medicine" or "I take less medicine than instructed" remained at roughly the same level at all three time points.

Preliminary statistical analyses did not reveal any statistically significant differences in terms of adherence between patients of different age, gender or social status (data not shown).

For the analysis of regimen complexity, 98 (t0), 85 (t1) and 71 (t2) medication regimens were included in the evaluation. Analysis of the latter time point (t2) was based either on the medication list returned by the GP ($n=7$) or by the

Table 1 Patient demographic characteristics

Variable	Data	Total *n*
Sex		108
Male	90 (83.3)	
Female	18 (16.7)	
Age (years)	63.1 (12.0)	96
Nationality		87
German	82 (94.2)	
Other	5 (5.8)	
Family status		83
Single	10 (12.0)	
Married	64 (77.1)	
Divorced	6 (7.2)	
Widowed	3 (3.6)	
Highest education completed		87
None or semi-skilled	7 (8.0)	
Professional school	11 (12.6)	
Completed apprenticeship	44 (50.6)	
College	25 (28.7)	
Professional status		90
Employed	27 (30.0)	
Unemployed	3 (3.3)	
Homemaker	1 (1.1)	
Retired	58 (64.4)	
Other	1 (1.1)	
Mean number (± SD) of diagnoses per patient	7.2 ± 5.3	100
Diagnoses[a]		100
Hypertension	81 (81)	
Diabetes mellitus type 2	27 (27)	
Hyperlipidemia	12 (12)	
Obesity	14 (14)	
Prostate cancer	15 (15)	
Other malignant tumours of genital tract	16 (16)	
Other additional diagnoses	99 (99)	
Ward		96
Urology	50 (52.1)	
Nephrology	33 (34.4)	
Endocrinology	13 (13.5)	
Length of stay, days (mean ± SD)	6 ± 4.4	95

SD, Standard deviation

Data are presented number of patients, with the percentage of the total ($n=108$) in parenthesis, except where indicated otherwise

[a] Multiple diagnoses possible

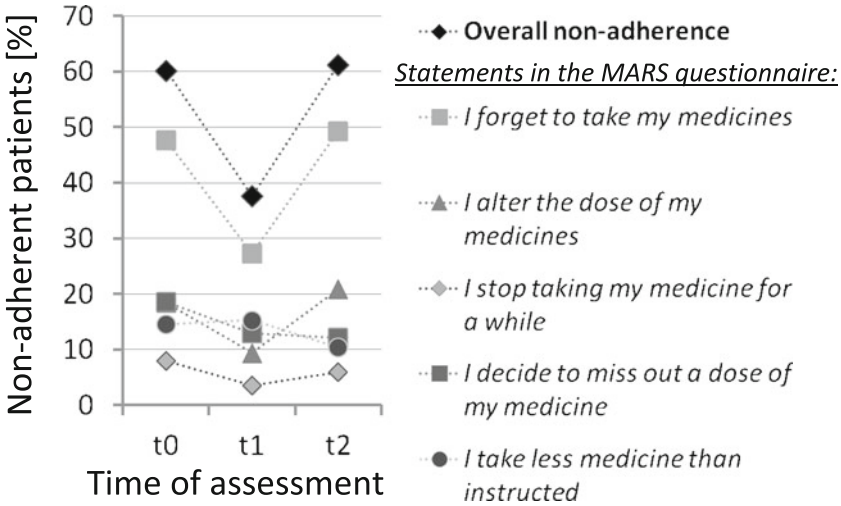

Fig. 1 Nonadherence according to the Medication Adherence Rating Scale–German version (*MARS-D*). The percentage of nonadherent patients was determined using the MARS-D questionnaire at three time points: *t0* at admission (outpatient care before the hospital stay), *t1* at discharge (inpatient care), *t2* 6 weeks after discharge from hospital (outpatient care after hospitalization). The different aspects and motives of unintended and intentional nonadherence are represented by the corresponding questions

patient (n=40) or both (n=24). Of the 24 doublets, 17 differed from each other. Missing regimens were due to incomplete files on the wards, absence of medication recommendations in discharge letters, transfer to wards not included in the study or failure to return questionnaires. The average regimen complexity at the three time points is shown in Fig. 2. The complexity of the hospital medication regimens differed little from the ambulatory regimens before and after the hospital stay. The overall complexity score was 13.27 ± 9.18 at t0, 13.72 ± 8.31 at t1 and 13.73 ± 9.70 at t2 (F=1.151,df=1, p=0.288; range 2–40). The average number of prescriptions [including medications to be taken "as-needed", excluding over-the-counter (OTC) medications] was 6.6 ± 3.93) at t0, 6.9 ± 3.74 at t1 and 6.7 ± 3.86 at t2 (F=1.248, df=1, p=0.269; range 1–18. The dosing frequency was slightly elevated in the hospital, but this was balanced by fewer additional drug administration directions being given concomitantly (not significant).

When asked about their attitudes towards their medication (Fig. 3), 68.6 % of the patients indicated that they "always" preferred taking as few tablets as possible although most did not regard the number of medications as a burden on their quality of life. Nevertheless, 39.3 % were willing to pay an additional charge for a reduction in the number of tablets to take. Of the patients, 5.7 % were frequently afraid of forgetting to take their medications or of taking their drugs incorrectly. More than half of the patients valued a distinguished appearance of the tablets to achieve correct administration, and 41.4 % regarded varying appearances of the same medication (tablets) as at least sometimes a potential cause for incorrect administration. Halving tablets was seen at least sometimes as a problem by 33.7 % of patients. In terms of the provision of medication in the hospital, 68.6 % of the patients stated that they were aware of the different drugs they received during their hospital stay (not shown), and 69.5 % of patients stated that a change of these drugs compared to their home medication never or seldom had an influence on their medication intake (not shown).

The GPs' responses to the questionnaire about the discharge medication are depicted in Fig. 4. Of the 108 patients

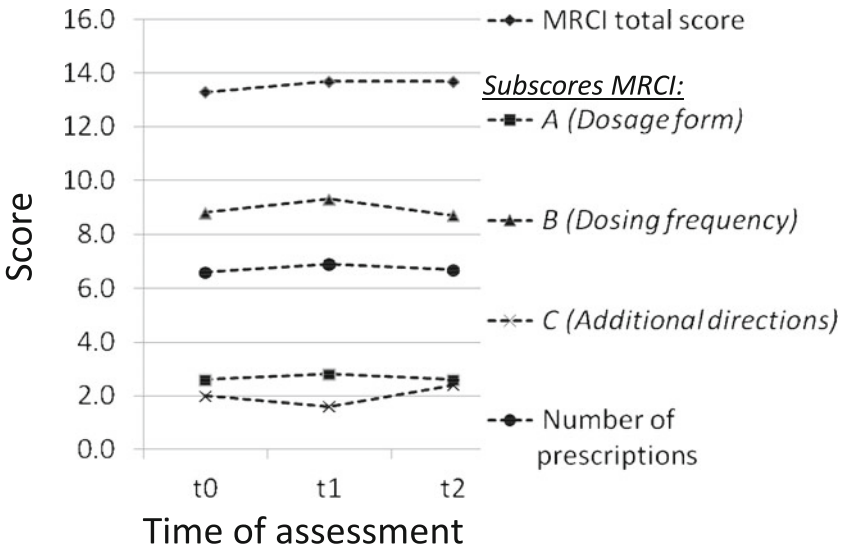

Fig. 2 Medication complexity according to the validated German version of the Medication Regimen Complexity Index (*MRCI-D*). Medication complexity was determined with the MRCI-D at three time points (*t0*, *t1*, *t2*). The different sub-scores were calculated for each medication in the regimen and then summed up as the total score. See caption to Fig. 1 for a description of the time points

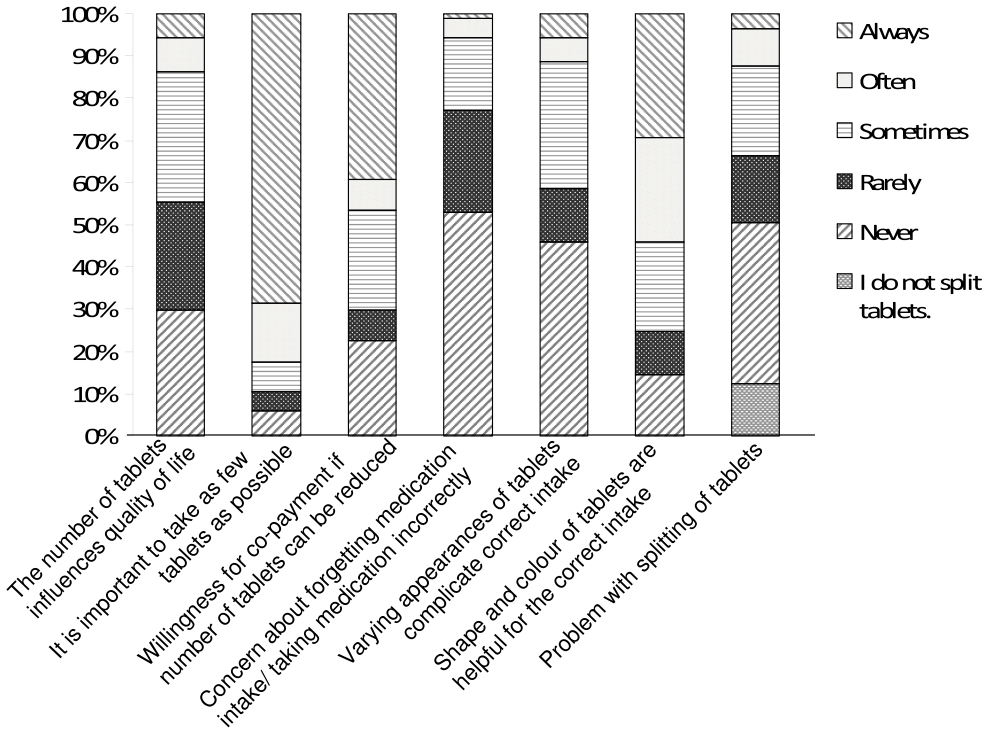

Fig. 3 Patients' attitudes towards medication. Patients were asked about their attitudes towards medication in a questionnaire at the time of admission (*t0*)

initially enrolled, 91 GPs were correctly identified and contacted by mail. The questionnaire was returned by 45 GPs, of whom 31 included the therapy plan of the respective patient. Professional medical experience was mainly between 11 and 20 and 21 and 30 years (37.2 and 32.6 %, respectively). Of the GPs who commented on the modifications in medications introduced in the hospital, two assessed these as much better, nine as better, seven as inferior and 19 as equal compared to the treatment before the hospital stay. Of the 45 GPs who returned the questionnaire, 76.8 % indicated that they always or often accepted drug prescriptions from hospital, although many stated to be restricted by their quarterly budgets that limit drug expenses. Willingness to prescribe more expensive drugs was dichotomous: one-half expressed such willingness as "always" or "often", the other half only as "sometimes", "seldom" or "never". The conviction that medication regimens should be as simple as possible was expressed by more than 80 % of the GPs, and nearly all were aware of the fact that halving tablets can be a problem for some patients. Nineteen GPs indicated to have modified the discharge medication for varying reasons (multiple choices possible), while another 19 stated to have continued with the recommended regimen from hospital (Fig. 5).

Discussion

Our study focused on the complexity as well as the adherence to medication regimens in a wide range of patients with chronic diseases in outpatient care *before* admission to hospital care, *during* hospital stay and in outpatient care 6 weeks *after* discharge. The definition of complexity included more facets than most other studies, which usually focus

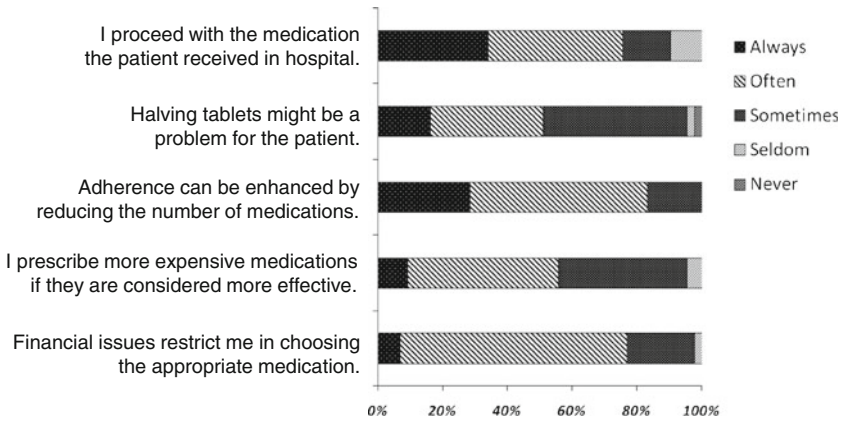

Fig. 4 General practitioners' (GPs) attitude towards prescriptions (validated percentage). GPs were asked about prescriptions ("To what extent do you agree with the following statements?") in a questionnaire sent to them 6 weeks after the respective patient had been discharged from the hospital (t2)

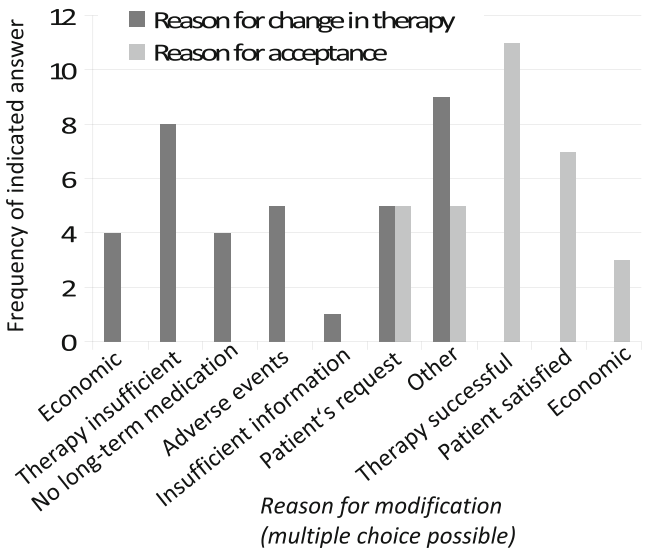

Fig. 5 General practitioners' reasons for acceptance/modification of hospital-recommended medication. GPs were asked about their reasons for modifying or accepting the medication recommended in the discharge letter in a questionnaire sent to them 6 weeks after the respective patient had been discharged from the hospital (t2); multiple choices were possible

on only one detail of complexity (for example, the number of medications to take or the number of daily doses) [27, 28]. We found that overall medication complexity did not change significantly over this period of time.

The complexity score found in our study is representative of a population of mainly hypertensive patients with few comorbidities. Compared to a sample of mainly diabetic patients [24], the complexity score is slightly lower in our study (15 vs. 13. respectively). This may be due to the fact that the addition of insulin to a medication regimen is associated with a distinct increase in complexity. A similar trend was seen in a study of patients with end-stage renal disease with a need for dialysis; the MRCI score was 22–28, depending on the dialysis procedure and medications taken [25]. The median number of medications at time of admission (6.6 at t0) in our study population is in agreement with findings reported earlier [30, 31].

It has been reported that the number of medications increase during a hospital stay [26]. Thus, we expected that medication complexity would also increase during the hospital stay in our study. However, both complexity and number of medications remained constant at the three time points. One reason for this result may be the inclusion of only long-term medications in our calculations. OTC products, which may complicate the therapy in the ambulatory sector, and temporary drugs added to the therapeutic regimen in the hospital, such as antibiotics or analgesics, were excluded in the analysis. Hence, the complexity score found in our study might underestimate the actual complexity.

At t0 the complexity calculations were performed on the basis of the pre-admission medication history as reported by the patients or documented in the medical files. In the past this method has frequently been reported to yield incomplete and discrepant information in medication reconciliation studies [27], leading to a further underestimation of complexity at this time point. Nevertheless, when assessing complexity with the aim of estimating its influence on adherence, it seems justified to rely on the medication details as perceived by the patient.

The percentage of nonadherent patients in outpatient care identified in our study (60.2 %) is in line with the adherence values of 26–59 % reported by Van Eijken et al. [28] but higher than those reported in other studies [29, 30]. It is difficult, however, to compare adherence results of different studies as they depend on the definition of adherence, assessment methods and patient populations. The population to which our findings can be considered applicable to is that of patients admitted to inpatient treatment with one or more chronic condition requiring antihypertensive medication. In terms of diagnoses and demographic characteristics, this is a heterogeneous group, but in terms of received treatment and setting this group can be considered to be homogeneous and representative of everyday routine care. This corresponds to our primary objective: investigating medication adherence under routine conditions from a healthcare services research perspective.

The method adopted in our study to measure adherence was by self-report even though the validity of self-reports has been criticized in the past based on frequent reports that self-reported adherence values tend to be higher than adherence values measured by, for example, the Medication Event Monitoring System (MEMS) or pill counting [31–34]. Also with the MARS-D, patients tended to overestimate their adherence [18]. It has therefore been postulated that self-report might be more powerful tool for identifying the nonadherer rather than adherer [35], which would also explain our results. Nevertheless, compared to the direct measurement of adherence, self-reporting is an inexpensive and pragmatic tool for the use in clinical practice.

A validation study of the MARS-D suggested defining a high cut-off value in order to increase the specificity of the questionnaire [32]. We followed this recommendation by choosing a high cut-off of 25. In a sample of mainly chronic obstructive pulmonary disease patients, nonadherence defined by the same cut-off was slightly higher (63 %) [20]. However, high cut-off values yield lower adherence rates because even the occasional failure to take the medication as advised is classified as nonadherence. Thus, studies with high cut-off values identify non-complete adherence rather than absolute nonadherence, and the patient may still benefit from therapy (although probably not to the maximum level).

Studies correlating the extent of medication adherence with medication effectiveness are warranted, and the results of such studies could help define clinical relevance-oriented cut-off values.

Nonadherence was mainly due to forgetfulness. Thus, adherence increased during hospital stay, where the supply of medications is more controlled, the intake supervised and the day scheduled with pre-determined meal times. Still, it did not reach 100 % in the hospital, possibly due to patient-related factors (e.g. no belief in medication) as well as circumstance-related ones (being absent in examinations, not feeling well).

The number of patients who were concerned about the varying appearances of their drugs was far lower than we expected. This might be due to a general "nonchalance" towards treatment, as deduced from the fact that less than 10 % were afraid of forgetting their medication or of taking it incorrectly. Also, insurance companies in Germany negotiate contracts with drug manufacturers on a quarterly basis, leading to frequent switches in the brand of medication taken by some patients, who apparently become accustomed to differently named and looking drugs. (This aspect of the study is specific to Germany and may differ from other countries with different healthcare systems and medication supply process.) Nevertheless, the majority of patients valued the appearance of their medications as being helpful for correct drug use.

Of note, the GPs stated insufficient effectiveness, patient request/satisfaction and costs as the main reasons for modifications of the discharge medication. Insufficient effectiveness and patient requests were expected factors as the treatment of hypertension requires the continuous adjustment of therapy and inclusion in the decision-making process is known to improve adherence [36]. The influence of economic issues might again be specific to Germany. However, the statements from the GPs have limited validity as the number of responses was low. GPs who disagreed with hospital-derived therapy modifications may have been less inclined to return the completed questionnaire, and both GPs and patients may have answered in a socially desirable way. To minimize the latter source of bias, questionnaires were anonymous and no reminders were made if questionnaires were not returned spontaneously [37].

Neither the MRCI nor the MARS showed a strong correlation between gender and total scores, which is in line with previous reports [20, 24]. Thus, our results are probably not biased due to gender distribution. Published data on associations between adherence and socio-demographic parameters are inconsistent [20]. In line with our findings, two studies did not find such correlations [20, 32]. In contrast, in another study, a slightly higher adherence was noted in older patients while patients living alone were less adherent [18].

In our analysis, we focused on medication complexity as a potential factor of influence on adherence. Other changes related to a transfer to hospital and back surely have an impact on patient adherence as well, but these were not the objective of this study. Further investigation is needed to see whether the medication complexity can be reduced in hospital and if this has a positive impact on patient adherence.

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