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Appropriateness and surveillance of medication in a cohort of diabetic patients on polypharmacy

S. Harder[1], K. Saal[2], E. Blauth[2], M. Beyer[2] and F.M. Gerlach[2]

[1]Institute for Clinical Pharmacology, [2]Institute for General Practice, University Hospital Frankfurt am Main, Germany

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Abstract. Context: It is assumed that with increasing polypharmacy, medication surveillance by the General Practitioner (GP) and adherence to the therapy regimen by the patient will both decline. Aim of the study: We evaluated clinical and medication records taken from GP documentations in a cohort of 102 diabetic patients (48 f, 54 m, median age 70, range 39 – 81) with 3 or more chronic prescriptions. Patients were asked about their current medication and its tolerability by means of a structured telephone interview. Results: 45% of the patients received up to 6 medications, 36% 7 – 9 and 19% > 10. The main comorbidity was hypertension (93%) and symptomatic CAD (39%). The use of established medications (β-blockers and ACE inhibitors) for these comorbidities was appropriate. Although 76% were eligible for a statin therapy, only 51% actually took a statin, and 28% had a dose lower than the defined daily dose. 68% of the patients had no prescriptions other than those recorded in the GP documentation, but 8% of the total number of medicines taken by the patients were not recorded in the GP's database. 62% of patients took all the medication prescribed by the GP, while 7% of all medicines recorded in the GP's database were not taken by the patients. In 10% of cases, an incompatible medication (defined in accordance with a consented list) was taken by the patient. 81% of patients regularly (twice per year) had their HbA1c checked, but only 62% had their potassium levels checked, despite the use of ACI and diuretics. Most patients knew the reason for taking at least one medication, but 18% knew this for less than half of their (multiple) medications. 70% of the patients said they had been informed about the possible risks of their medication by the GP, and 7% knew the risks for only one medication. Conclusion: In this cohort of patients on polypharmacy and with a high risk profile for adverse drug reactions, we found a mismatch between GPs' documentation of prescriptions and the medication taken by the patient. Patients had no detailed knowledge about indications and almost no knowledge about risks. Although the overall performance of therapy (appropriateness) was deemed sufficient, there would appear to be room for improvement in order to fill information gaps and strive for stricter surveillance.

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Correspondence to
Prof. Dr. med. S. Harder
Institute for Clinical Pharmacology
Pharmazentrum Frankfurt
University Hospital
Frankfurt/Main
Theodor Stern Kai 7
60590 Frankfurt am Main, Germany
harder@em.uni-frankfurt.de

Introduction

Inappropriate prescriptions and polypharmacy are threatening for patients, e.g. as a result of drug-drug or drug-disease interactions [Bergk et al. 2004, Juurlink et al. 2003], and the level of inappropriate prescriptions was found – depending on the criteria and state of the disease – to be between 15 and 80% of all medications [Fialova et al. 2005, Stuck et al. 1994]. On the other hand it has been convincingly demonstrated that drug therapies for major cardiovascular diseases (e.g. left ventricular dysfunction after myocardial infarction, hyperlipidemia in coronary heart disease) have clear benefits for patients, although this inevitably leads to polypharmacy [Boyd et al. 2005]. However, it can be assumed that with increasing polypharmacy, medication surveillance by the General Practitioner (GP) and adherence to the therapy regimen by the patient will both decline. Furthermore, in case of multimorbidity, GPs may neglect emerging indications in cases of well-established therapy regimens [Kuijpers et al. 2008]. Epidemiological data indicate a lack of adherence to therapy guidelines in the prescription of, for example, angiotensin-converting enzyme inhibitors, β-blockers or statins, or anticoagulants – especially in polymedicated patients [Feely et al. 2000, Harder et al. 2001, Roe et al. 2000]. Furthermore, several therapies require that certain laboratory values (creatinine, potassium) be checked in order to avoid medication risks [Baglin et al. 1995]. It

Table 1. Demographics (n = 102 patients).

Age	Median 70 (range 39 – 81)
Gender	48 female/54 male
Main Morbidities	
NIDDM	62
IDDM	40
CAD	31
CHF	16
Hypertension	85
Prior stroke	19
HbA1c*	median 6.6 % (Range 5.0 – 10.0)
Creatinine-Clearance	median 84 ml/min (range 120 – 16)

*last value (n = 83 patients with this information available in GP's records). **calculated from last value for creatinine i.S. by Cockcroft and Gault formula (n = 83 patients with this information available in GP's records).

was the aim of the following survey to assess prescription quality and medication surveillance in a group of patients with several comorbidities. We evaluated clinical and medication records taken from GP documentations, and asked the patients about their medication.

Methods

As the survey was planned to be a preparatory study with the aim of methodically analyzing the problems of polypharmacy outlined above, we restricted the diversity of possible multimedication by requiring that patients included in the survey should receive at least 1 antidiabetic drug (oral antidiabetic or insulin). Furthermore, only patients that regularly took 3 or more other drugs (of which at least 1 should not be an antihypertensive drug) were included. We, therefore, first selected patients from the GP databases that had at least 1 prescription for an antidiabetic agent, and then chose those patients with more than 3 chronic prescriptions (n = 102). Data on chronic diagnoses (ICD-10), prescriptions, laboratory values and diagnostic reports from specialists were collected retrospectively for a period of one year. Altogether eight GPs in the region of Frankfurt am Main (Germany) participated in the survey, and the number of patients included by each GP varied from 5 to 14. The demographic characteristics and values for HbA1c as well as their creatinine clearance (calculated from creatinine serum levels by the Cockcroft and Gault formula) of the cohort are given in Table 1.

After data collection in the practice, a semistructured telephone interview was performed with the patients. Patients were asked about all their medication (as written on the box), how they were using it (dosage, method of administration), the reason for taking it, their knowledge of possible risks and their experiences with tolerability. This interview was carried out 1 – 2 months after data had been collected from the GP and was done so by final-year MD students under the supervision of an MD. The study was approved by the IRB of the Frankfurt University Hospital, and written informed consent was obtained from the patients for their participation in the study, as well as for study personnel to access their data in their GPs database.

The appropriateness of the medication was evaluated using a set of explicit criteria: the presence of contra-indications according to the summary of medicinal product characteristics (Fachinformation), the adherence to dosing recommendations in case of renal impairment (according to the "Fachinformation"), and the adherence to some basic principles of cardiovascular therapy, commonly distributed to the medical public at the start of the observation period in 2005 [Harder et al. 2005, Komajda 2003]. Furthermore, a set of rules for the surveillance of the therapy (laboratory controls) was established [Munar and Singh 2007]. These principles and rules are presented in Tables 2 and 3, together with the results. Furthermore, statements made by the patients regarding their medication were compared with the prescriptions documented by the GP. A mismatch was calculated as the number of medications quoted by the patient but not documented by the GP, non-adherence was calculated as the number of prescriptions documented by the GP but not mentioned by the patient. Patients were asked about the reason for receiving the prescription and the possible risks associated with it. Statements were accepted as valid when the patient correctly assigned the prescription to a certain disease (e.g., high BP), an organ system (e.g., coagulation, kidney) or a symptom ("pain", "water"). Expected answers to questions about risks were, for example, "bleeding" (with NSAIDs or oral anticoagulant (OAC)), heart beat disturbances (with glycosides) and "loss of salts" (with diuretics).

Table 2. Drugs prescribed most often according to ATC group (data from GPs records) and over the counter (OTC) medications (as quoted in the patient's interview).

ATC-Code	Drug class	% patients with a prescription
A02B	Proton Pump Inhibitors	16
A10A	Insulin	39
A10B	Anti-diabetic (oral)	73*
B01A A	Oral anticoagulant	10
B01A C	Antiplatelet agent	50
C03A B	Diuretic	12
C07A, C07B	Beta-blocking agent (+/- diuretic)	61
C09A, C09B	Angiotensin converting enzyme inhibitor (+/- diuretic)	54
C09C, C09D	Angiotensin receptor blocker (+/- diuretic)	22
C10A A	Statin	49
M01A	Non-steroidal anti-inflammatory drug	8
N06A	Anti-depressive agent	12
various OTCs	Vitamins supplements (38% of total OTCs), magnesium (17% of total OTCs), various phytopharmacological preparations (33 % of total OTCs), ibuprofen or aspirin [500 mg] (12 % of total OTCs)	60

*33% metformin alone; 20% sulfonylurea-derivative [glimeperide, glibenclamide] alone; 10% oral combination (metformin with sulfonylurea or metformin/rosiglitazone), 10% combination oral agent with insulin.

Table 3. Adherence to Guidelines.

Criterion	Frequency (% patients, n = 102)		
	yes (%)	no (%)	n.a. (%)*
Betablocker after documented myocardial infarction (except proven/documented contraindication or intolerance)	13	2	85
ACE-Inhibitor or ARB after documented myocardial infarction (except proven/documented contraindication or intolerance)	12	3	85
ACE-Inhibitor or ARB after documented congestive heart failure (except proven/documented contraindication or intolerance) (in parentheses: percent of patients at target dose)	14 (7)	1	85
Betablocker after documented congestive heart failure (except proven/documented contraindication or intolerance) (in parentheses: percent of patients at target dose)	12 (8)	3	85
Antiplatelet after TIA/stroke	15	3	82
Aspirin (100 mg) in hypertensive diabetic patients	54	29	17
Secondary prevention in patients with documented coronary artery disease and/or stroke with a statin (in parentheses: percent of patients with DDD prescribed)	51 (28)	25	24

* Disease condition not present.

Statistics

This survey had an exploratory purpose, and no hypothesis was specified. Therefore, data were entered into a Microsoft ACCESS 2000 database and analyzed descriptively.

Results

62 patients had an NIDDM, 40 patients were on insulin. The main co-morbidities were hypertension (85 patients) and symptomatic coronary artery disease CAD (31 patients) (Table 1).

dicated medications (n = 21 medications) were found. 81% of patients had their HbA1c levels checked regularly (twice per year), and poor control (defined as HbA1c > 8.5%) was seen only in 11% of the patients. However, only 62% had regular checks for their potassium levels, despite the use of ACI and diuretics (Tables 4, 5). Although 81% had their serum creatinine levels measured regularly, only 35% had their creatinine clearance calculated and documented in the GP's file.

68% of patients only received prescriptions recorded in the GP documentation, 17% received 1 prescription, 9% 2 prescriptions and 7% > 2 prescriptions which were not found in the GP documentation. Overall, 8% of all medicines taken by the patients were not recorded in the GP's database (i.e. mismatch). All the medication prescribed by the GP was actually taken by 62% of patients, while 19% took all but 1, 9% all but 2 and 6% all but > 2 medication prescribed by the GP. Overall, 7% of all medicines recorded in the GPs database were not taken by the patients (i.e. non-adherence).

Most patients knew the reason for at least one of the drugs there were taking and only 18% knew why for fewer than half of their (multiple) medications. On average, 80% of all medications were correctly assigned. 70% of patients said they had been informed by their GP about the possible risks associated with their medication, but only 7% were able to name at least one risk. A total of 98% had no complaints about their therapy.

Discussion

Our data from Germany are basically in close agreement with reports from other western countries, and the size of the cohort is similar to those in other in-field observations [Okuno et al. 1999, Rottlaender et al. 2007, Siu et al. 1996]. The morbidity profile in this cohort is representative of elderly, diabetic subjects [Kerek-Bodden et al. 2000]. The number of ambulatory prescriptions (median 7) is similar to observations of comparable patient cohorts, including diabetic patients [Harder et al. 2005, Okuno et al. 1999, Rottlaender et al. 2007]. However, although several GPs were involved, the region was restricted to the vicinity of Frankfurt am Main. Furthermore, GPs had to provide their consent to the cooperation and had also been involved in previous research studies carried out by the institute. Thus, there may have been a positive selection bias and it is not certain that the sample was representative in terms of the GPs' prescription behavior.

In contrast to older reports [Komajda et al. 2003, Roe et al. 2000], we found a good penetration rate for ACE inhibitors and β-blockers in patients with myocardial infarction or chronic heart failure. As reported earlier by our group [Harder et al. 2001, 2005], the penetration rate of statins was only fair and doses fell short of the DDD range. The underprescription of statins is, for example, also a common phenomenon in other EU countries [Feely et al. 2000]. Patients without statin prescriptions all had hyperlipidemia and a preceding cardiovascular event, a situation in which the benefit of lipid-lowering therapy seems beyond doubt [Lewis 2004]. We also found a relatively low level of inappropriate prescriptions (3%) when based on the contraindications quoted in the "Fachinformation". This is at variance with our own previous data from cardiovascular patients from 1997, when the level of inappropriate prescriptions was 21% [Harder et al. 1998], and a former study in which we found that about 30% of elderly multimorbid patients had at least one inappropriate prescription [Harder et al. 2005]. Even higher numbers (up to 80%) are reported from investigations relying on pharmacy or insurance prescription data [Coste and Venot 1999, Meredith et al. 2001]. However, these reports were based on an evaluation using Beers' criteria, which were not applied to our data since we did not only include elderly patients (the focus was on polypharmacy). Furthermore, the appropriateness and importance of these criteria to the contemporary European drug market is taken into consideration [Laroche et al. 2007a,b].

Diuretics can trigger potentially harmful water and electrolyte balance disorders. The elderly are particularly vulnerable to these side effects, which include orthostatic hypotension, hyponatremia, severe dyskalemia and functional renal failure [Palmer et al. 2003]. Hyperkalemia and an increase in creatinine are also matters of concern when using ACI or ARB [Long et al. 2004], especially in patients with preexisting renal impairment.

Careful clinical supervision and serum chemistry monitoring are, therefore, required (fluid balance, sodium and potassium blood levels and renal function) [Baglin et al. 1995, Munar and Singh 2007]. We found that about 12% of patients on diuretics and/or ACI had no regular creatinine measurements, and in those whose creatinine was measured, the actual creatinine clearance was not calculated. Furthermore, 30% of patients eligible for the routine determination of their potassium levels were unable to provide information on these. A recent report on data obtained from the French health insurance data transfer system (SIAM) showed that in a cohort of 13,000 elderly patients (> 75 years) on diuretic therapy, approximately 20% had not had any serum chemistry measured within the past year [Gerardin-Marais et al. 2008]. Another recent survey on physicians' behavior with regard to creatinine clearance (CC) measurements in elderly patients showed that, although most GPs said that they take CC into account, few actually calculated it (18%) and most, therefore, underestimated the severity of renal impairment [Jonville Bera et al. 2008].

One should expect all of a patient's prescribed drugs to appear on the GPs' records. A level of approximately 8% of mismatched prescriptions (i.e. not in the GPs database but claimed to have been taken by the patients) is quite low, and may also be due to the fact that the GP records are not updated frequently enough. We are not able trace the prescription of these drugs to the prescriber. Some of them may originate from specialists, outpatient clinics, or hospital departments. Our data on the level of agreement between patients and GPs' prescriptions is considerably better than previously estimated in a German survey [Junius-Walker et al. 2007]. In that survey, which was based on a questionnaire and not on prescription data, doctors and polymedicated patients agreed on the same number of prescribed drugs in only 43% of cases. In general, doctors underestimated the number of consumed medications.

Although knowledge about the reason for taking a particular medication was satisfactory in 82% of patients, only a few could describe the possible risks and caveats involved. These data are in agreement with a recent German report [Harder et al. 2005] and other reports [Cullen et al. 2006, Okuno et al. 1999, Papanikolaou et al. 2003]. Obviously there has been no improvement in recent years, but this fact should not be disregarded as an ipso facto phenomenon inherent in a health system. It is also not solely a German phenomenon. A report from Denmark showed that only 60% of polymedicated patients knew why they were taking a particular medication, 21% knew the consequences of omission of the drugs, but less than 6% knew about the toxic risks, side effects and potential drug interactions [Barat et al. 2001]. However, it has been claimed that limited knowledge about medication risks contributes towards medication misadventures [Barat et al. 2001, Cullen et al. 2006] and, in general, low health-related literacy has been shown to be a predictor for enhanced mortality [Baker et al. 2007].

In conclusion, in this cohort of patients on polypharmacy and with a high risk profile for adverse drug reactions, we found a mismatch between GP documentations of prescriptions and the medication the patient said he was taking. There is no thorough knowledge about indications and almost no knowledge about risks. Although the overall performance of therapy (appropriateness) is adequate and obviously patients were satisfied, there is room for improvement to fill information gaps and strive for stricter surveillance.

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