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ORIGINAL RESEARCH ARTICLE

Self-Medication with Over-the-Counter and Prescribed Drugs Causing Adverse-Drug-Reaction-Related Hospital Admissions: Results of a Prospective, Long-Term Multi-Centre Study

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Abstract
Background Self-medication, including both the use of over-the-counter (OTC) drugs and the use of formerly prescribed drugs taken without a current physician's recommendation, is a public health concern; however, little data exist regarding the actual risk.
Objective We aimed to analyse self-medication-related adverse drug reactions (ADRs) leading to hospitalisation.
Methods In a multi-centre, observational study covering a hospital catchment area of approximately 500,000 inhabitants, we analysed self-medication-related ADRs leading to hospital admissions in internal medicine departments. Data of patients with ADRs were comprehensively documented, and ADR causality was assessed using Bégaud's algorithm. The included ADRs occurred between January 2000 and December 2008 and were assessed to be at least 'possibly' drug related.
Results Of 6,887 patients with ADRs, self-medication was involved in 266 (3.9 %) patients. In 143 (53.8 %) of these patients, ADRs were due to OTC drugs. Formerly prescribed drugs and potential OTC drugs accounted for the remaining ADRs. Most self-medication-related ADRs occurred in women aged 70–79 years and in men aged 60–69 years. Self-medication-related ADRs were predominantly gastrointestinal complaints caused by non-steroidal anti-inflammatory drugs (most frequently OTC acetylsalicylic acid [ASA, aspirin]). In 102 (38.3 %) of the patients

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For the German Network of Regional Pharmacovigilance Centres.

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with self-medication-related ADRs, a relevant drug–drug interaction (DDI), occurring between a self-medication and a prescribed medication, was present (most frequently ASA taken as an OTC drug and prescribed diclofenac).

Conclusion In the general population, self-medication plays a limited role in ADRs leading to hospitalisation. However, prevention strategies focused on elderly patients and patients receiving interacting prescribed drugs would improve patient safety.

Key Points

Self medication accounts for approximately 4 % of ADR-related hospitalisations to internal medicine departments.

OTC-drugs and formerly prescribed drugs taken without a current physician's advice contribute almost equally to self-medication-related ADRs.

ADR-prevention strategies should focus on elderly patients and patients receiving multiple medications for long-term, particularly those taking NSAIDs, oral anticoagulants and antiplatelet drugs.

1 Introduction

Non-prescription drugs constitute a substantial part of the total drug consumption in the general population. For example, in Germany, about 677 million packages of over-the-counter (OTC) drugs compared with 734 million packages of prescription (Rx) drugs were distributed by pharmacies in 2011 [1]. In the past, only well-established drugs that had been on the market for many years were available as OTC drugs; however, in recent years, many modern and highly efficacious drugs like proton pump inhibitors, statins, levonorgestrel, and triptans were switched to OTC status in some European countries. For example, a yearly increase in such Rx-to-OTC switches has been reported for the UK [2]. In Germany, omeprazole became available as a non-prescription drug in 2009, and several analgesic drugs have undergone Rx-to-OTC switches in the past (e.g. ibuprofen 400 mg has been a non-prescription drug since 1998). Since ibuprofen 400 mg is also available as a prescription drug, this medication, as well as others that are available both OTC and by prescription, are considered as 'potential OTCs'.

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Many authors view this increase in the personal responsibility of patients as something positive [3], but several concerns have arisen regarding adverse drug reactions (ADRs) caused by self-medication. For example, analgesics taken as self-medication have been described as harmful, particularly in elderly patients [4]. Additionally, a drug–drug interaction (DDI) between a self-medication and a prescribed medication might increase the risk for developing an ADR [2, 5].

Patients' risk awareness is lower with respect to OTC drugs than for drugs prescribed by physicians [6]. Not surprisingly, a remarkable number of consumers take OTC drugs for longer and even in higher doses than recommended in the package insert without consulting a physician [6, 7]. As all drugs have the potential for adverse reactions, it is of great interest to evaluate the safety profile of OTC drugs. However, there are few safety data available for OTC drugs. This may be due to several methodological difficulties regarding the assessment of drug exposure and ADRs. Prescription databases—which are widely used for analysing ADRs associated with Rx drug utilization—can not be used for OTC drugs. Thus, pharmacy-centred studies are required, but a complete medication history is difficult to obtain in this setting. Non-recognition of OTC drugs as 'drugs' by patients, and incomplete medical histories taken by physicians, may contribute to uncertainties in evaluating OTC drug-related ADRs [8].

Furthermore, another aspect of self-medication that is sometimes overlooked is that people may use a formerly prescribed medication at a later point in time, without informing their physician. Thus, although self-medication is defined as the use of non-prescription drugs (OTC drugs) by most authors [2], a different definition that has been proposed includes the use of formerly prescribed drugs taken at a later time point without a physician's recommendation [9]. This type of self-medication, namely the intake of formerly prescribed drugs, has only been examined for a limited number of medications [10]. Given the dearth of information regarding ADRs caused by both types of self-medication, our goal was to analyse ADRs leading to hospitalisation with a particular emphasis on both formerly prescribed drugs and OTC drugs. This analysis was performed using data from a previously described long-term observational study [11, 12].

2 Methods

For this study, we analysed data from the German Network of Regional Pharmacovigilance Centres (NRPC). During the study period (January 2000 to December 2008), the NRPC consisted of six study centres. Four centres, situated at university or teaching hospitals in Rostock, Greifswald,

Jena, and Weimar, were responsible for ADR detection and data collection. Quality assurance and statistical analyses were performed by the remaining two centres in Wuppertal and Munich. The study was approved by the responsible ethics committees.

An ADR leading to hospital admission was defined, in accordance with World Health Organization (WHO) guidelines, as a "response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function" [13]. In addition, we included medication errors that lead to hospital admissions and that reflected clinically relevant 'real–life' problems such as the non-consideration of renal function for renally excreted drugs or the non-consideration of the maximum recommended daily dose in OTC drugs. Patients with severe cutaneous reactions were not included in our study so as to avoid confusion with an established reporting system [14]. In addition, we excluded patients receiving chemotherapy, suicide attempts, and patients under the age of 17 years.

As described elsewhere [12], all four ADR collecting centres screened non-elective hospital admissions to departments of internal medicine. The ADRs leading to these admissions were identified by (i) systematic screening of admissions to emergency rooms and departments of internal medicine and (ii) spontaneous reports from physicians in the internal medicine departments. Clinical pharmacologists and pharmacists trained in pharmacovigilance screened admission protocols using a list of trigger symptoms frequently related to an ADR, which has been described in detail [15].

In patients suspected of having ADRs, drug exposures including self-medication (OTC drugs or formerly prescribed Rx drugs) were assessed by chart reviews and patient interviews. Hence, we could analyze whether a suspicious ADR was caused by a drug prescribed by a physician and taken by the patient appropriately (non-self-medication) or by self-medication. For ease of reading, the term 'Rx-drugs' is used for 'non-self-medication' and the term 'self-medication' is used for both 'formerly prescribed Rx drugs' (e.g. antibiotics left over from a previous infection) and OTC drugs (e.g. ibuprofen 200 mg). Rarely, a particular dose could be both prescribed and available as OTC (e.g. ibuprofen 400 mg). If the patient was unsure as to whether the drug was received by prescription or OTC, then classification into one of two main categories (formerly prescribed drug or OTC) was made based upon the patient's knowing the brand name. If the patient could not remember the brand name, then the drug was considered a 'potential OTC drug' within the category of 'self-medication'. All drugs were coded using the Anatomical Therapeutic Chemical (ATC) classification system [16].

For all suspected ADRs, a causality assessment was performed for each drug taken before admission using Bégaud's algorithm [17]. According to the algorithm, the causal association between drug and ADR was classified as 'very likely', 'likely', 'possible' or 'dubious'. All suspected ADRs were comprehensively documented, including demographic data, past medical history, and medications taken, in a pseudonymized manner in an ACCESS™ database according to the data protection and privacy policies stated in the study approval. The documented data from the ADR-suspected patients were used to define the number of drugs taken or number of diseases present at admission. ADRs were coded according to MedDRA® [18], and ADR type, severity, and outcome were assessed using established algorithms [19–21]. MedDRA®, the Medical Dictionary for Regulatory Activities, terminology is the international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The MedDRA® trademark is owned by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) on behalf of ICH. For all suspected ADRs, quality assurance including discussion of disagreements, e.g. discordant assessment of ADR causality and data inconsistencies, were performed daily. All disagreements and inconsistencies were resolved by consensus. In addition, regular case discussions by phone and face-to-face meetings were conducted in order to provide for a high-quality, long-term study. After quality assurance, all documented ADRs were reported to the Federal Institute for Drugs and Medical Devices (BfArM, Bonn, Germany).

In this study, we analysed the following variables for patients with an at least 'possible' ADR according to Begaud's algorithm: age, sex, number of diseases present at hospital admission, number of drugs taken at hospital admission, number of ADR-suspected drugs, length of hospital stay, type and outcome of ADR and number of patients receiving analgesic self-medication stratified by treatment duration.

All metric and normally distributed variables were reported as mean ± standard deviation; non-normally distributed variables were presented as median (first–third quartile). Categorical variables were presented as frequency and percentage. For the comparison of groups, the Mann–Whitney *U* test was used for metric variables and the chi-squared test or Fisher's exact test was used for categorical variables. *P* values <0.05 were considered statistically significant. All statistical calculations were performed using SAS statistical software package, version 9.2 (SAS Institute Inc., Cary, NC, USA) or R version 3.0.2 (R Core Team, R Foundation for Statistical Computing.

A Language and Environment for Statistical Computing. Wien, Austria, http://www.R-project.org).

3 Results

3.1 Patients

During the study period, approximately 212,000 patients were admitted to the internal medicine departments of the study hospitals. Out of these admissions, 6,887 (approximately 3.2 %) patients were hospitalised with 7,406 ADRs assessed as at least 'possible'. In most patients ($n = 6{,}621$; 96.1 %), the ADRs were caused by Rx drugs only. In 266 patients (3.9 % of all patients with ADRs, Fig. 1), self-medication contributed causally to an ADR. Out of these 266 patients, OTC drugs were assessed as ADR causative in 143 patients, whereas formerly prescribed drugs and potential OTC drugs accounted for ADRs in 122 and 14 patients, respectively (see Fig. 2; in 13 patients, ADRs were attributed to more than one self-medication category).

As shown in Table 1, in comparison with patients with Rx drug-related ADRs, patients with self-medication-related ADRs leading to hospital admission were younger, more often male, had fewer diseases, took fewer medications, and had a shorter length of hospital stay. However, the highest absolute number of self-medication-related ADRs occurred in women aged 70–79 years and in men aged 60–69 years. Since younger patients had a much lower absolute number of Rx drug-related ADRs, the fraction of patients with self-medication-related ADRs out of all patients with ADRs was consequently highest in younger patients, reaching more than 25 % in males under the age of 30 years (Fig. 3). Further stratifications of patient characteristics with self-medication-related ADRs ($n = 266$) with respect to the type of causative self-medication (formerly prescribed Rx drugs, potential OTCs, OTCs, or a combination of these types) are shown in Electronic Supplementary Table 1.

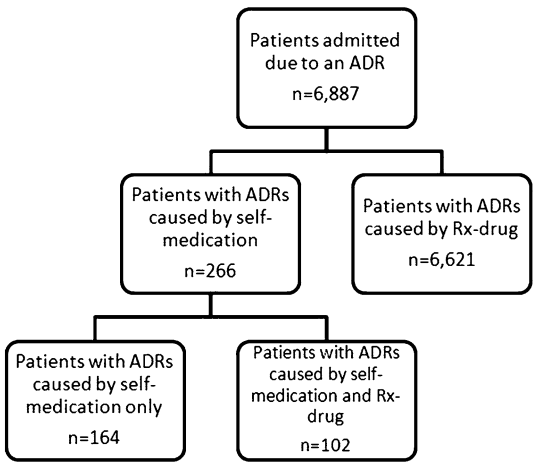

Fig. 1 Flow chart of study patients according to adverse drug reaction-causative medication. *ADR* adverse drug reaction, *Rx* prescription

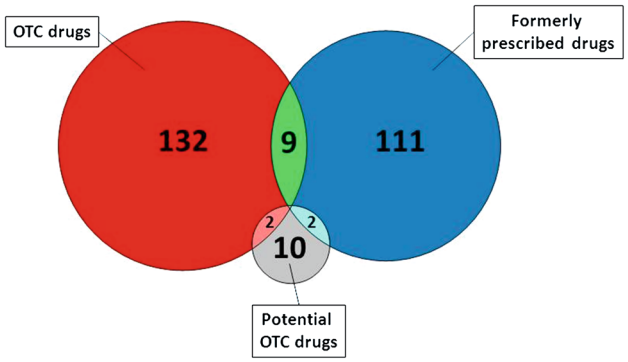

Fig. 2 Venn diagram of causative drugs in patients with adverse drug reactions due to self-medication ($n = 266$). *OTC* over the counter

3.2 Characteristics of Adverse Drug Reactions (ADRs)

When comparing ADRs caused by self-medication ($n = 282$) with ADRs caused by Rx drugs ($n = 7{,}124$) some remarkable differences became obvious. For example, idiosyncratic type B reactions were more common in patients with self-medication-related ADRs (20.2 vs. 9.1 %, $p < 0.0001$). Further stratifications for ADR type according to self-medication type (formerly prescribed Rx drug, potential OTC, and OTC) are presented in Electronic Supplementary Table 2. With respect to ADR affected organ classes, 'immune system disorders', particularly allergic reactions, were more commonly observed in patients with self-medication-related ADRs as compared with Rx drug-related ADRs (8.2 vs. 1.7 %). In both patient groups, ADRs affected most frequently the gastrointestinal tract, usually as gastrointestinal bleeding (self-medication 59.9 %, Rx drugs 35.3 %). Of note, 90 patients (1.3 %) with Rx drug-related ADRs died, but only one patient (0.4 %) died due to a self-medication-related ADR ($p = 0.27$). This patient died shortly after hospital admission from a massive gastrointestinal haemorrhage caused by ibuprofen (self-medication) and phenprocoumon (a prescription-only vitamin K antagonist).

3.3 Causative Drugs

ADRs associated with Rx drugs were caused in the majority of cases by antithrombotic agents (ATC group B01), followed by drugs used in diabetes (A10) and

Table 1 Patient demographics and characteristics

	ADRs caused by Rx drugs only	ADRs caused by at least one self-medication drug	*p* value
Patients	6,621 (96.1)	266 (3.9)	
ADRs	7,124	282	
Age, y	70.7 ± 15.3	58.9 ± 19.3	<0.0001*
Women	3,978 (60.1)	133 (50.0)	0.001**
No. of diseases [median (Q1–Q3)]	5.0 (3.0–6.0)	3.0 (1.0–5.0)	<0.0001*
No. of drugs [median (Q1–Q3)]	6.0 (4.0–9.0)	3.0 (1.0–6.0)	<0.0001*
No. of suspected drugs [median (Q1–Q3)]	2.0 (1.0–2.0)	1.0 (1.0–2.0)	0.0018*
Length of hospital stay, days, [median (Q1–Q3)]	8.0 (5.0–13.0)	7.0 (3.0–11.0)	<0.0001*

Data are presented as *n* (%) or mean ± SD unless otherwise indicated

ADR adverse drug reaction, *Q1* first quartile, *Q3* third quartile, *Rx* prescription, *SD* standard deviation

* Mann–Whitney *U* test/** chi-squared test

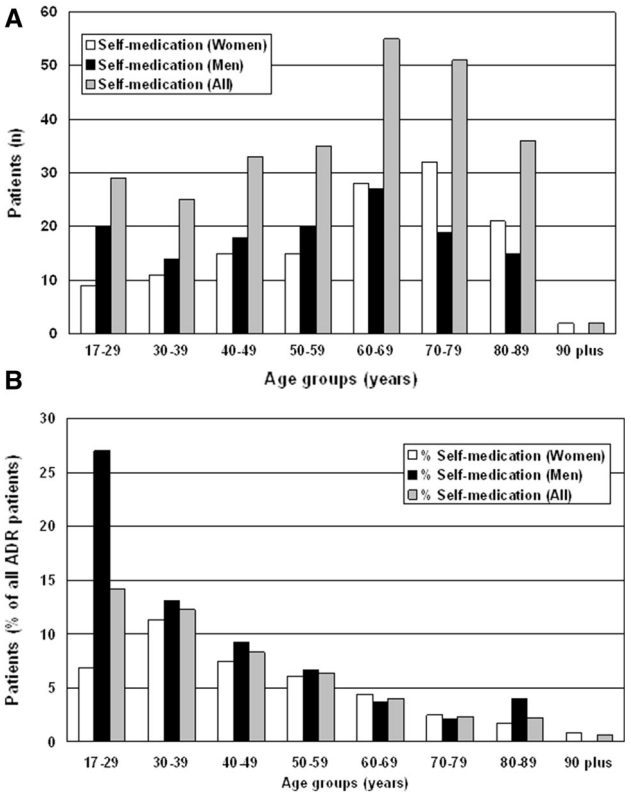

Fig. 3 *Top* number of patients with adverse drug reaction caused by self-medication stratified by age groups and sex, *Bottom* percentage of patients with adverse drug reaction caused by self-medication (out of all adverse drug reaction patients) stratified by age groups and sex. *ADR* adverse drug reaction

diuretics (C03). We separated patients with self-medication-related ADRs into those caused by self-medication only ($n = 164$) and those caused by interactions between self-medication and Rx drugs ($n = 102$) (Fig. 1).

3.4 Self-Medication Only

In the patients with ADRs caused by self-medication only ($n = 164$), acetylsalicylic acid (ASA) taken as an analgesic compound was causative in 45 patients (27.4 %), followed by diclofenac and ibuprofen ($n = 22$ [13.4 %] each). ASA used as an analgesic was the OTC medication with the most ADRs ($n = 45$ patients), whereas the formerly prescribed drug taken as self-medication with the largest number of ADRs was diclofenac ($n = 21$) (Table 2). Further details regarding particular ADRs for different types of self-medication are presented in Electronic Supplementary Table 3.

With respect to non-analgesic drugs, self-medication with low-dose ASA (antithrombotic indication, mainly as a formerly prescribed Rx drug), glyceryl trinitrate (formerly prescribed Rx drug), and glibenclamide (formerly prescribed Rx drug) caused ADRs in ten, five and three patients, respectively (Table 2). In 20 patients, DDIs between different self-medications were found to have caused the ADR. A concomitant intake of two analgesic ASA preparations was uncovered in three patients, and a concomitant intake of diclofenac and analgesic ASA was found in two patients. For the remaining DDIs resulting in self-medication only ADRs, please see Electronic Supplementary Table 4.

3.5 Concomitant Use of Self-Medication and Prescription Drugs

A total of 102 patients were admitted due to ADRs resulting from the concomitant use of self-medication and Rx drugs. The most frequent self-medication interacting with Rx drugs was analgesic ASA ($n = 34$ patients) in combination with prescribed diclofenac ($n = 11$ patients).

Table 2 Number of patients receiving drugs causing self-medication-related adverse drug reactions (self-medication only) stratified by type of self-medication

Drug [ATC (7-digit)][a]	Total (n[b])	OTC	Potential OTC	Formerly prescribed Rx drug
Acetylsalicylic acid (N02BA01)	45	45 (100)	0	0
Diclofenac (M01AB05)	22	0	1 (4.5)	21 (95.5)
Ibuprofen (M01AE01)	22	8 (36.4)	7 (31.8)	7 (31.8)
Paracetamol (acetaminophen), combinations excl. psycholeptics (N02BE51)	16	14 (87.5)	0	2 (12.5)
Low-dose acetylsalicylic acid (B01AC06)	10	2 (20.0)	0	8 (80.0)
Acetylsalicylic acid, combinations excl. psycholeptics (N02BA51)	7	7 (100.0)	0	0
Dipyrone (metamizole sodium, N02BB02)	6	0	0	6 (100.0)
Glyceryl trinitrate (C01DA02)	5	0	0	5 (100.0)
Paracetamol (acetaminophen, N02BE01)	5	5 (100.0)	0	0
Glibenclamide (A10BB01)	3	0	0	3 (100.0)
Furosemide (C03CA01)	2	0	0	2 (100.0)
Sildenafil (G04BE03)	2	0	0	2 (100.0)
Naproxen (M01AE02)	2	2 (100.0)	0	0
Propyphenazone (N02BB04)	2	2 (100.0)	0	0
Other drugs	36	17 (47.2)	0	19 (52.8)

Data are presented as n or n (%) unless otherwise indicated

ATC anatomical chemical classification, *OTC* over the counter, *Rx* prescription

[a] Drugs with one case only are shown in the group 'Other drugs'

[b] n exceeds the number of patients with self-medication-only ADRs ($n = 164$ patients [$n = 144$ patients with one self-medication, $n = 20$ patients with self-medication drug–drug interaction]) due to a patient being counted more than once if receiving more than one ADR-causative drug

Table 3 Number of patients with drug–drug interactions (three most frequent adverse drug reaction-causative self-medication) and interacting prescription drugs (ATC [7 digit])

Self-medication (patients)[a]	Rx drugs[b] (patients)
Acetylsalicylic acid (N02BA01) ($n = 34$)	Diclofenac (M01AB05) ($n = 11$), low-dose acetylsalicylic acid (B01AC06) ($n = 8$), ibuprofen (M01AE01) ($n = 7$), phenprocoumon (B01AA04) ($n = 4$), meloxicam (M01AC06) ($n = 4$), dexibuprofen (M01AE14) ($n = 2$), acetylsalicylic acid (N02BA01) ($n = 2$), gingko biloba (N06DX02) ($n = 2$)
Diclofenac (M01AB05) ($n = 19$)	Low-dose acetylsalicylic acid (B01AC06) ($n = 7$), phenprocoumon (B01AA04) ($n = 2$), clopidogrel (B01AC04) ($n = 2$), torsemide (C03CA04) ($n = 2$), erythromycin (J01FA01) ($n = 2$)
Ibuprofen (M01AE01) ($n = 8$)	Low-dose acetylsalicylic acid (B01AC06) ($n = 2$)

Rx prescription

[a] The same compound (e.g. diclofenac, low-dose acetylsalicylic acid) could be assessed differently depending on the patient's drug history

[b] The table includes only drugs with more than one case

Diclofenac taken as self-medication was found to be ADR causative in 19 patients, most frequently in combination with prescribed low-dose ASA, which was being used as an antiplatelet agent ($n = 7$ patients) and phenprocoumon ($n = 2$ patients) (Table 3). The most relevant Rx drugs that interacted with analgesic ASA, diclofenac, and ibuprofen taken as self-medication were other non-steroidal analgesics or antithrombotic drugs (primarily low-dose ASA) and anticoagulants (mainly phenprocoumon); please see Electronic Supplementary Table 5.

3.6 Focus on Analgesics Taken as Self-Medication

Since most self-medication-related ADRs were caused by analgesics (irrespective of concomitant medication), we analysed this drug class in more detail ($n = 190$ patients). We found that most analgesics causing self-medication-related ADRs were OTCs ($n = 122$ patients) followed by formerly prescribed analgesics ($n = 62$) and potential OTCs ($n = 13$, with some patients counted more than once). A total of 29 patients were receiving a fixed-

Table 4 Treatment duration before occurrence of adverse drug reaction and patients with a treatment duration >4 days for analgesic drugs taken as self-medication (single compounds only)

Compound (ATC)	Patients (*n*)	Duration in days [median (Q1–Q3), min–max]; (patients[a] with an exact treatment duration)	Patients taking analgesics for >4 days [*n* (%)] (patients[a])
Acetylsalicylic acid (N02BA01)	79	6.0 (1.0–60.0), 1.0–9422.0 ($n = 65$)	51 (64.6) ($n = 79$)
Diclofenac (M01AB05)	41	17.0 (5.0–105.0), 1.0–7398.0 ($n = 30$)	32 (82.1) ($n = 39$)
Ibuprofen (M01AE01)	30	8.0 (3.0–60.0), 1.0–3768.0 ($n = 24$)	20 (71.4) ($n = 28$)
Dipyrone (metamizole sodium) (N02BB02)	10	5.0 (1.0–19.5), 1.0–920.0 ($n = 8$)	5 (62.5) ($n = 8$)
Paracetamol (acetaminophen) (N02BE01)	9	2.0 (1.0–4.0), 1.0–13,911.0 ($n = 7$)	1 (14.3) ($n = 7$)
Others	12	66.0 (23.0–998.0), 1.0–5349.0 ($n = 9$)	8 (72.7) ($n = 11$)
All	161[b]	8.0 (2.0–73.0), 1.0–13,911.0 ($n = 145$)	117 (68.0) ($n = 172$)

ATC anatomical chemical classification, *Q1* first quartile, *Q3* third quartile

[a] For some patients, only a rough estimate of treatment duration was documented (e.g. 'for years'). Thus, the number of patients included for analyzing patients taking analgesics for >4 days could exceed the number of patients for whom an accurate calculation of treatment duration was performed

[b] Since patients could receive more than one compound, the sum of patients exceeds the total number of patients ('all')

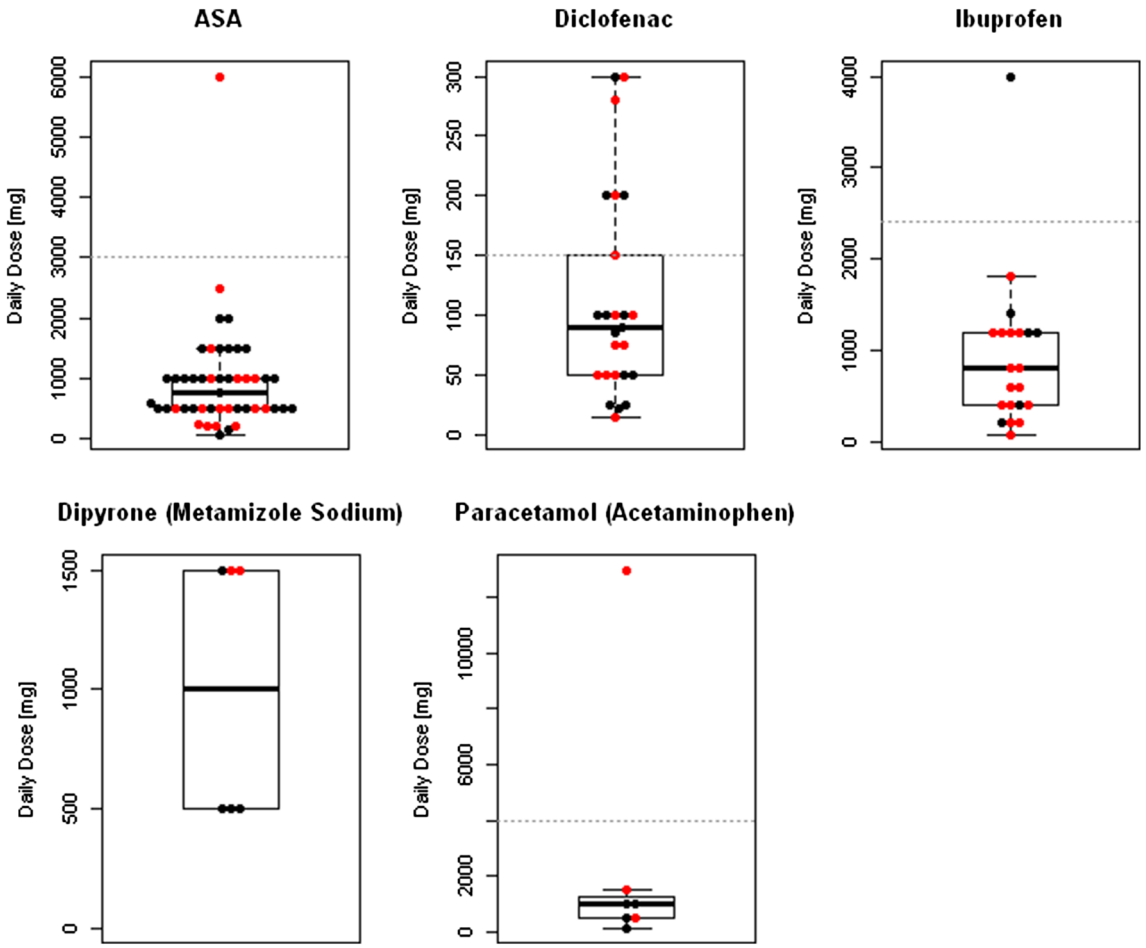

Fig. 4 Daily doses of analgesic drugs taken as self-medication (*red* indicates females, *black* indicates males, *dotted line* indicates the recommended maximum daily dose [ASA: 3,000 mg, diclofenac: 150 mg, ibuprofen: 2,400 mg, dipyrone (metamizole sodium): 4,000 mg (not shown), paracetamol (acetaminophen): 4,000 mg]). *ASA* acetylsalicylic acid

combination drug. For the remaining 161 patients, ASA was the causative agent in most patients, followed by diclofenac and ibuprofen (Table 4).

Regarding the effect of sex in this group of 190 patients, we found no significant differences between men and women in the number of ADRs caused by formerly prescribed drugs or OTCs. For example, for analgesic ASA, we found that 7 of 12 ADRs (58.3 %) were caused by formerly prescribed ASA and 36 of 86 ADRs (41.9 %) were caused by ASA taken as an OTC drug occurred in women ($p = 0.36$).

A median intake of 8 days (Q1–3: 2.0–73.0 days) before ADR occurrence was found for analgesics taken as self-medication. The recommended treatment duration of 4 days for analgesic self-medication (according to German package inserts) was exceeded in 68 % of patients (Table 4). Whereas most immune disorders (mainly allergic reactions) occurred within the first 4 days of treatment (76.9 vs. 23.1 %), the majority of gastrointestinal disorders occurred after more than 4 days (28.3 vs. 71.7 %). We found significant differences regarding the ADR pattern comparing both time intervals (up to 4 vs. more than 4 days, $p = 0.0002$). The recommended daily dose was exceeded in nine patients (diclofenac [formerly prescribed Rx drug]: $n = 6$, acetylsalicylic acid [OTC], ibuprofen [potential OTC], and paracetamol [acetaminophen] [OTC]: each $n = 1$; Fig. 4).

4 Discussion

Since 2004, patient safety has been on the WHO agenda [22] and is part of the national health action plans in many countries, e.g. in the USA (national patient safety goals) [23] and Germany (action plan for optimization of drug safety) [24]. As Pirmohamed et al. [25] have shown in their milestone study, approximately 6.5 % of hospital admissions are due to ADRs. More recently, ADR prevalence rates leading to hospitalisation were reported in a systematic review to be between 0.2 and 15.7 % [26]. In our study, we observed a relatively low rate of approximately 3.2 % ADR-related hospital admissions [11], which might be related to focusing on ADRs leading to hospital admissions into departments of internal medicine (i.e. we did not capture drug-induced bone fractures, haematuria).

In terms of methodology, we used an approach similar to that of Olivier et al. [4] and so included formerly prescribed drugs taken without current medical advice in our definition of self-medication. Of all the ADR-related hospital admissions found in our study, self-medication was deemed causative in only 3.9 % of the 6,887 patients. By examining a much smaller sample of 66 patients aged ≥65 years, Olivier et al. [4] found that self-medication was causative for hospital admissions in three patients. In that multivariate analysis, self-medication did significantly increase the risk for ADR-related hospital admissions (odds ratio [OR] 2.34; 95 % confidence interval [CI] 1.18–4.66). In addition, the number of drugs being taken and the use of antithrombotics and antibiotics were other risk factors for ADR-related hospital admissions [4].

In our analyses, similar numbers of men and women suffered from self-medication-related ADRs. Given that Beitz et al. [27] reported a slightly higher prevalence of OTC drug use for women than for men in Germany (approximately 40 vs. 30 %), we expected to find a higher prevalence of OTC-related ADRs in women in our study. Among many possible explanations for these discrepant results, sex-specific differences in the compounds used as OTC drugs should be considered. For example, in terms of analgesics, Paulose-Ram et al. [28] showed, in a sample of US adults, that men use ASA more frequently, whereas women use ibuprofen and paracetamol more frequently. By transferring the US data to Germany and by taking into account a lower gastrointestinal bleeding risk for paracetamol and ibuprofen than for ASA [29], our results, showing no relevant sex-related differences for self-medication-related ADRs, seem reasonable.

In our study, the absolute number of self-medication-related ADRs leading to hospitalisation was highest in elderly patients. However, according to drug consumption data from both Germany and the USA, younger and middle-aged individuals are the most likely to be OTC users [27, 28, 30]. Although an international comparison of OTC drug use is impeded by several differences (e.g. drugs and drug dosages available without prescription, questionnaires used in surveys), these data and our findings highlight the generally acknowledged fact that elderly patients are at higher risk for ADRs [31], regardless of the prescription status. Well known age-related issues such as altered pharmacokinetics and pharmacodynamics, multimorbidity, and polypharmacy might contribute to the higher vulnerability of the elderly for ADRs.

In our study, gastrointestinal complaints were the most frequent ADRs occurring with self-medication and, in most cases, ASA, diclofenac, and ibuprofen were the causative compounds. Confirming our data, Hasford et al. [7] found abdominal pain and discomfort to be the most frequent ADRs in patients taking diclofenac as self-medication. In a pharmacy-based survey conducted in Germany, exceeding the recommended treatment duration or consuming incorrect dosages were major aspects of OTC drug-related problems [32]. Particularly for OTC medications, pharmacists play an important role in reducing OTC-related ADRs by assessing a patient's drug history and comorbidities before selling a drug [32]. In a meta-analysis of three retrospective case control studies, non-steroidal anti-

inflammatory drug (NSAID) treatment (excluding ASA) for more than 4 days during the most recent week, or using high doses, led to an increased adjusted OR for serious gastrointestinal complaints [33]. For ASA, a similar risk increase has been found in a prospective cohort study [34]. However, the relative risk for gastrointestinal complications is lower after OTC NSAID usage than after prescribed NSAID usage, which can be explained by the lower permitted doses used in OTC preparations for several NSAID compounds [35]. In our study, we found that analgesic self-medication was taken for more than 4 days in approximately two-thirds of ADR patients, whereas exceeding the recommended dose was less frequently reported.

DDIs between Rx drugs and self-medication have been a matter of concern for many years [2, 5]. Regarding our results, concomitant intake of self-medication and Rx drugs was found to be ADR causative in 38 % of patients with self-medication-related ADRs (1.5 % of the total sample). In a large internet-based survey covering five European countries, a concomitant intake of Rx drugs and OTC analgesics was present in approximately 12 % of patients suffering from pain [36]. Our data have shown that the concomitant use of antithrombotics (e.g. mainly low-dose ASA) or oral anticoagulants (e.g. warfarin) and a NSAID is relevant for gastrointestinal bleeding as reported previously in a systematic review [5]. In our study, only a few patients were found to be taking two or more NSAIDs but due to a lack of data regarding exposed patients not having an ADR, it was not possible to examine how this affected gastrointestinal bleeding risk. However, a meta-analysis of patients using multiple NSAIDs has reported an adjusted OR >20 for upper gastrointestinal bleeding in such patients [37].

Besides analgesics, other compounds were of minor importance for self-medication-related ADRs in our analysis. In most of these cases, ADRs were caused by formerly prescribed glyceryl trinitrate, glibenclamide, furosemide and sildenafil. Thus, it should be kept in mind that patients may store prescribed drugs at home and use them later without medical advice. Moreover, a Slovenian survey of patients has found that drug sharing among relatives and friends may occur [38].

From a healthcare provider's perspective, more attention should be given to patients receiving Rx drugs and OTC drugs concomitantly. From a drug authority's point of view, a clearer statement of maximum single and daily dosages as well as treatment durations in OTC package inserts may help to achieve a better risk–benefit ratio. The second type of self-medication (formerly prescribed drugs) could be possibly reduced by prescribing more appropriate package sizes and by public campaigns explaining the risks of taking medications without a physician's advice.

Our study approach has some limitations. We included ADRs leading to internal medicine department hospital admissions. Thus, ADRs that required admission to dermatological, neurological, or other medical specialties were not covered by our approach. In particular, patients with gastrointestinal bleeding who were primarily treated in a surgical department were only included if a referral to an internal department was later made. Nevertheless, most patients with gastrointestinal bleeds are treated in internal medicine departments.

Another limitation is that OTC drug consumption data are unavailable for our hospital catchment areas, therefore, an estimate of OTC-related ADR incidences is not feasible. Also, OTC-related ADR prevalence rates may be higher or lower in countries with differing OTC drug markets and consumption. For example, ibuprofen is available as an OTC drug in Germany up to a dose of 400 mg (but there are also some 400 mg preparations that are Rx drugs), whereas in other countries (e.g. Spain) higher ibuprofen doses are sold without a prescription. On the other hand, analgesic ASA, which is an OTC drug in Germany, can be prescribed to some patients with severe pain receiving opioids. Nevertheless, some economic aspects might have influenced self-medication-related issues. During the study period, fees have to be paid for physicians' visits and for drugs prescribed by physicians in Germany. Hence, in some cases (e.g. low-cost drugs like ASA), patients may decide to get ASA as an OTC drug in order to save money. Consequently, there may be a few patients receiving ASA first as an OTC medication and subsequently as a Rx drug, or vice versa. This may limit the validity of our OTC-related ADR analysis to some extent due to the latency in developing ADRs such as gastrointestinal bleeds.

In our study, we used a conservative approach for estimating the number of patients suffering from self-medication-related ADRs caused by exceeding recommended dosages. For example, we used a daily maximum dose of 2,400 mg for ibuprofen, whereas in several summary of product characteristics (SPCs), which cover a variety of medication, a range of 1,200–2,400 mg is given for the daily maximum dose of ibuprofen. For diclofenac, we used a threshold of 150 mg (recommended dose in Rx formulations [75 mg]) instead of a threshold of 75 mg (recommended dose in OTC formulations [12.5 mg]) since almost all patients suffering from self-medication-related ADRs caused by diclofenac received diclofenac as a prescribed drug. It follows that the number of patients found to have taken an excessive dose would be higher in studies using lower daily maximum dose thresholds.

Finally, we analysed self-medication by combining OTC drugs and formerly prescribed drugs. Although possibly considered a limitation, the complexity of this analysis of self-medication reflects the 'real-world' use of medications

more accurately and comprehensively than focusing on OTC drugs only. By separating both main types of self-medication, we found that OTC drugs were responsible for ADRs in 143 patients (53.8 %), which underscores the importance of these drugs. However, we also found that formerly prescribed drugs taken as self-medication accounted for a significant number of ADRs.

As in all studies analysing ADRs, causality assessment remains an issue. In our study we used Bégaud's algorithm [17, 39], which has been demonstrated to be a sensitive and specific method to detect ADRs [40], particularly when used by experienced assessors. Moreover, ADRs were extensively documented in our database and causality assessment was a subject of quality control in all cases. Despite some new algorithms and methods developed recently [41, 42], a 'gold standard' is still missing for assessing ADR causality.

This study collected the data prospectively and provided an independent quality control of all ADRs by clinical pharmacologists. The frequencies and profiles of self-medication-related hospital admissions presented here should reflect a valid picture of the problem.

5 Conclusion

To the best of our knowledge, we report here for the first time the results of a long-term, prospective, multi-centre observational study that focused on two forms of self-medication, specifically, OTC drugs and formerly prescribed drugs. In terms of self-medication-associated hospital admissions, analgesics taken as OTC drugs are of greatest relevance compared with other OTC drug classes or formerly prescribed drugs. Nevertheless, self-medication accounted only for a very small fraction of identified drug-related hospital admissions to general internal medicine services. However, the somewhat restrictive German OTC drug policy might contribute to the low number of OTC drug-related ADRs in our study. For countries with a wider spectrum of OTC drugs (and higher OTC dosages), an increased risk for OTC drug-related ADRs has to be expected. In particular, elderly patients and patients with DDIs (predominantly between OTC and prescribed antithrombotic drugs [mainly low-dose ASA]) are at risk for OTC-related ADRs. For both types of self-medication, further research is required for a better understanding of drug safety issues in a real-life setting.

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