Gender-Based Differences in Drug Prescription: Relation to Adverse Drug Reactions

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Key Words

Adverse drug reactions, risk • Drug prescription • Gender differences

Abstract

Background/Aim: The female gender appears to suffer from more adverse drug reactions (ADRs) than the male gender. So far, there has been no epidemiologic study analyzing gender-based differences in drug prescribing and its ADR risks. The aim of the present study was to establish a drug risk stratification adjusted to age, number of prescriptions and drug classes with respect to gender differences based on intensive data acquisition methods. **Method:** A prospective multicenter study was conducted in several departments in Germany and Israel (pediatrics, medicine and geriatrics) enclosing 2,371 inpatients. **Results:** A total of 25,532 drug prescriptions during hospitalization were evaluated. At least 1 ADR was found in 774 patients (32.6%). Drugs for the cardiovascular system, nervous system, alimentary tract and musculoskeletal system were prescribed most often in females. The following drug classes led significantly more often to ADRs in women as compared to men: alimentary tract (OR 0.5; $p = 0.0002$), cardiovascular system (OR 0.72; $p = 0.0140$), musculoskeletal system (OR 0.31; $p = 0.0004$) and nervous system (OR 0.62; $p = 0.0023$). After adjustment to

age, total number of prescriptions and drug class, only anti-infectives (antibacterials) and musculoskeletal system (anti-inflammatory) drugs stand out as causing more ADRs in women. **Conclusion:** Antibacterials and anti-inflammatory agents cause more ADRs in females as compared to males.

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Introduction

Adverse drug reactions (ADRs) impact on patients' quality of life and sometimes have fatal consequences. The female gender appears to suffer from more ADRs than the male gender [1–5]. However, the cause of this phenomenon remains unclear. On the one hand, differences in drug pharmacokinetics and pharmacodynamics have been suspected of being responsible factors [6–8]. On the other hand, gender differences in anaphylactoid reactions and drug-induced cardiac arrhythmias including torsade de pointes indicate that other factors – in contrast to kinetics and body composition – may be decisive for the occurrence of ADRs [9, 10]. Some investigators, however, argue that higher ADR rates in females are mainly due to higher prescription rates of certain drug classes, e.g. antidepressants [11, 12].

So far, there is no epidemiological study that identifies groups with gender-specific medication risks. One problem is the recruitment of a study population that is large enough to be analyzed for ADRs. It is also difficult to identify confounding factors such as age, amount of prescriptions and class of drugs.

In this study we attempted drug risk stratification by gender after adjustment to age, amount of prescriptions and class of drugs on the basis of intensive prospective multicenter drug surveillance.

Methods

Design of the Study

Over a 2-year period, a prospective multicenter study, based on intensive pharmacovigilance, was conducted in several departments (pediatrics, medicine and geriatrics) at the Friedrich Alexander University of Erlangen-Nuremberg, the Hadassah University of Jerusalem, the General Hospital Waldkrankenhaus St. Marien of Erlangen and the University Hospital of Regensburg including a total of 2,371 hospitalized patients. All admissions were monitored prospectively for the occurrence of ADRs by a pharmacoepidemiological team (PETE) consisting of physicians, pharmacologists and pharmacists. Patient charts were screened and bedside visits took place on a daily basis for detection and evaluation of potential ADRs. If there was disagreement about the definition of a particular event as an ADR, a fourth physician, pharmacist or pharmacologist, was involved and the event discussed until a consensus was reached. All ADRs were classified with respect to probability, severity and preventability; causative drugs and therapeutic consequences were identified and all information was entered into a specifically developed database named KLASSE [13].

Patient Characteristics. Patients were evaluated based on their demographic data (age and gender), number and class of drugs prescribed.

Documentation and Classification of Drugs according to ATC [14]. All drugs prescribed between admission and discharge were documented in KLASSE and classified by the Anatomical Therapeutic Chemical Classification System for Human Medicine (ATC) [14]. This system classifies drugs into groups at 5 different levels: the first level is the anatomical group and consists of 1 letter. There are 14 main groups, which are shown in table 1. The second level of the code is based on the therapeutic main group and consists of 2 digits. Agents that are not included in the ATC system are summarized in category V (various). For statistical analysis, the first and second levels of the ATC code were used (table 1).

Definitions and Characteristics of ADRs

ADRs were defined according to the adverse reaction terminology of the WHO [15]. Additionally, all ADRs were categorized into 6 different reactions:

Type A. Dose-related reactions, which are common, and related to the augmented pharmacological action of the drug. Examples are toxic effects or side effects.

Table 1. ATC first level and its therapeutic main groups

Anatomical group	Therapeutic group
Blood and blood-forming organs (B)	anticoagulants, antiplatelets, thrombolytics
Cardiovascular system (C)	antiarrhythmics, antihypertensives, diuretics, vasodilators, antianginals, beta-blockers, angiotensin-converting enzyme inhibitors, antihyperlipidemics
Skin (D)	emollients-antipruritics
Reproductive system (G)	hormonal contraception, fertility agents, selective estrogen receptor modulators, sex hormones
Endocrine system (H)	antidiabetics, corticosteroids, sex hormones, thyroid hormones
Infections and infestations (J, P)	antibiotics, antivirals, vaccines, antifungals, antiprotozoals, anthelmintics
Malignant and immune disease (L)	anticancer agents, immunostimulators, immunosuppressants
Muscles, bones, and joints (M)	anabolic steroids, anti-inflammatories, antirheumatics, corticosteroids, muscle relaxants
Brain and nervous system (N)	anesthetics, analgesics, anticonvulsants, mood stabilizers, anxiolytics, antipsychotics, antidepressants, nervous system stimulants, sedatives
Respiratory system (R)	bronchodilators, decongestants, H ₁ antagonists

Type B. Non-dose-related reactions are uncommon and not related to a typical pharmacological action of the suspected drug. Examples are immunological or idiosyncratic reactions.

Type C. Dose- and time-related reactions are uncommon effects related to the cumulative dose of a drug such as hypothalamic pituitary adrenal axis suppression of corticosteroids.

Type D. Time-related reactions are delayed reactions that occur some time after the use of the drug such as teratogenesis or tardive dyskinesia.

Type E. Withdrawal symptoms become apparent after the early withdrawal of a drug, for example lung edema after stopping diuretics or opiate withdrawal syndrome.

Type F. Unexpected failure of therapy is mainly due to inadequate dosage of drugs or the prescription of dangerously interacting drugs.

The probability of ADRs was evaluated by PETE using the Naranjo Score Algorithm. Doubtful ADRs were excluded from statistical consideration [16].

Severity was assessed by applying a weighted score of the following indicators of drug-induced harm: whether ADRs impaired the patient's quality of life, caused temporary or permanent inability to work, led to or prolonged hospitalization, caused temporary or permanent malfunction of an organ system, were dangerous, life-threatening or fatal. An additional criterion was that if withdrawal of the drug or introduction of a different drug therapy was necessary. A score of 1–4 indicates a mild ADR, 5–8 a moderate and >8 a severe ADR [17]. Mild, moderate and severe ADRs were included in our consideration.

Some patients had several ADRs simultaneously or successively, hence the total number of ADRs in our analysis is greater than the total number of patients having a reaction. If more than one drug was considered to be responsible for causing an ADR, the most probable drug was used for analysis and statistics.

Statistical Analysis

Data were first analyzed using descriptive statistical methods. Depending on the scale applied, the (variable) mean together with the corresponding standard deviation (SD) or the median with the range (Q25/Q75) was given. We used the t test or the Mann-Whitney-Wilcoxon's U test to compare the distribution of continuously distributed variables, and the χ^2 test for categorical variables.

The rate of prescription of the anatomical group (ATC) according to gender was adjusted to the total amount of prescriptions and the age of patients. The occurrence of ADRs was adjusted to the amount of prescriptions, age and anatomical group (ATC).

We employed the SAS system version 9 (SAS Institute, Inc., Cary, N.C., USA). The study was conducted after getting permission from the ethics commission and was supported by the ELAN-Foundation of the University Hospital Erlangen.

Results

Patient Characteristics

Altogether, a total of 2,371 patients were included in the study. The number of females was 1,012 (42.7%). Mean age of the study population was $55.3 \pm$ (SD) 26.7 years (range 41–76). Males were significantly younger than females ($p < 0.001$) with a mean age of $52.8 \pm$ (SD) 25.1 years (range 39–71) and $58.6 \pm$ (SD) 28.4 years (range 44–80), respectively.

Prescriptions

A total of 25,532 drugs were prescribed for the study population during hospitalization (11.4 ± 10.2). The median number of drugs prescribed for each patient was 9 (5/15). The median number of drugs prescribed for females was 11 (6/16) and 9 for males (5/14, $p < 0.0001$).

In total, most prescriptions were issued for medications belonging to the following ATC classes: A ($n = 1,978$), N ($n = 1,723$), B ($n = 1,464$) and C ($n = 1,435$).

Groups A ($n = 863$), B ($n = 693$), C ($n = 666$), D ($n = 39$), H ($n = 370$), M ($n = 349$), N ($n = 763$) and S ($n = 49$) showed significantly more prescriptions in female patients.

Due to the existing variations of age in the study population, data were adjusted according to age and number of prescriptions for each anatomical group (ATC). It turned out that women received significantly more prescriptions of drugs from groups B (OR 0.75; $p = 0.008$), H (OR 0.49; $p < 0.0001$) and M (OR 0.62; $p < 0.0001$). For men, group J prevailed (OR 1.26; $p = 0.0115$).

Table 2 shows an overview of gender-specific prescriptions on the basis of the first level of the ATC code (anatomical group).

Adverse Drug Reactions

In 774 (32.6%) out of 2,371 patients, at least 1 ADR was found by the team. Altogether 1,773 ADRs were observed. 413 females (40.8%) and 361 males (26.6%) encountered at least 1 ADR, altogether 986 and 787 ADRs were documented, respectively.

Using the Naranjo score, ADRs were termed possible in 40.7% (female) and 36.8% (male), probable in 54.2 and 59.7%, respectively, and very probable in 5.1 and 3.6%, respectively. The degree of severity was mild in 56.2% (female) and 57.5% (male), moderate in 42.0 and 39.8%, respectively, and severe in 1.8 and 2.7%, respectively.

Table 3 shows the gender-specific distribution of ADR-inducing prescriptions grouped according to the first level of the ATC code (anatomical groups).

Prescriptions associated with the highest rate of ADRs in our study population were from anatomical groups (ATC) C ($n = 269$), N ($n = 184$), J ($n = 143$) and A ($n = 129$).

For females, most ADRs were induced by prescriptions from groups C ($n = 143$), N ($n = 101$), A ($n = 77$) and M ($n = 44$). For males, groups C ($n = 126$), N ($n = 83$), J ($n = 74$) and A ($n = 52$) led to most ADRs.

Medications from ATC groups A (OR 0.5; $p = 0.0002$), C (OR 0.72; $p = 0.0140$), M (OR 0.31; $p = 0.0004$) and N (OR 0.62; $p = 0.0023$) were significantly more often associated with ADRs in women. In order to minimize potential confounding factors, adjustment according to age, total number of prescriptions and ATC class (first and second level) was carried out. This resulted in a differentiated picture, i.e. only prescriptions from classes J and M showed a significantly higher risk of inducing ADRs. In our population, the therapeutic main groups within the above-mentioned anatomical groups (ATC) were antibacterials (J; $n = 1,003$) and anti-inflammatory

Table 2. Number of prescriptions of a certain main drug class, gender-based distribution, crude and adjusted to total amount of prescribed drugs and age of subjects

Drugs, ATC first level	n (% of all)	F, n (%) ¹	M, n (%) ¹	OR not adjusted	p	OR adjusted	p
A Alimentary tract and metabolism	1,978 (83.4)	863 (85.3)	1,115 (82.1)	0.79 (0.63–0.99)	0.036	1.04 (0.81–1.35)	NS
B Blood and blood-forming organs	1,464 (61.8)	693 (68.5)	771 (56.7)	0.60 (0.51–0.72)	<0.0001	0.75 (0.60–0.93)	0.0089
C Cardiovascular system	1,435 (60.5)	666 (65.8)	769 (56.6)	0.68 (0.57–0.80)	<0.0001	0.93 (0.74–1.16)	NS
D Dermatologicals	72 (3.0)	39 (3.9)	33 (2.4)	0.62 (0.39–0.99)	0.0473	0.69 (0.43–1.12)	NS
G Genitourinary system and sex hormones	201 (8.5)	93 (9.2)	108 (8.0)	0.85 (0.64–1.14)	NS	1.08 (0.80–1.46)	NS
H Systemic hormonal preparations, excluding sex hormones and insulins	650 (27.4)	370 (36.6)	280 (20.6)	0.45 (0.37–0.54)	<0.0001	0.49 (0.40–0.59)	<0.0001
J Anti-infectives for systemic use	1,036 (43.7)	438 (43.3)	598 (44.0)	1.03 (0.87–1.21)	NS	1.26 (1.05–1.52)	0.0115
L Antineoplastic and immunomodulating agents	198 (8.3)	90 (8.9)	108 (8.0)	0.88 (0.66–1.18)	NS	0.95 (0.70–1.28)	NS
M Musculoskeletal system	649 (27.4)	349 (34.5)	300 (22.1)	0.54 (0.45–0.65)	<0.0001	0.62 (0.51–0.75)	<0.0001
N Nervous system	1,723 (72.7)	763 (75.4)	960 (70.6)	0.79 (0.65–0.94)	0.0103	1.0 (0.82–1.23)	NS
P Antiparasitic products, insecticides and repellents	42 (1.8)	20 (2.0)	22 (1.6)	0.82 (0.44–1.50)	NS	0.95 (0.51–1.77)	NS
R Respiratory system	650 (27.4)	292 (28.9)	358 (26.3)	0.88 (0.74–1.06)	NS	1.04 (0.86–1.27)	NS
S Sensory organs	79 (3.3)	49 (4.8)	30 (2.2)	0.44 (0.28–0.70)	0.0006	0.67 (0.41–1.08)	NS
V Various	303 (12.8)	120 (11.9)	183 (13.5)	1.16 (0.90–1.48)	NS	1.19 (0.89–1.61)	NS

NS = Not significant.

¹ The percentage given refers to the overall number of the relevant gender.**Table 3.** Occurrence of ADR within gender, adjusted to total amount of prescribed drugs, age of subjects and type of drug class

Drugs, ATC first level	ADR, n (%)	F, n (%) ¹	M, n (%) ¹	OR not adjusted	p	OR adjusted	p
A Alimentary tract and metabolism	129 (6.5)	77 (8.9)	52 (4.7)	0.50 (0.35–0.72)	0.0002	0.73 (0.50–1.08)	NS
B Blood and blood-forming organs	102 (7.0)	54 (7.8)	48 (6.2)	0.79 (0.52–1.18)	NS	0.81 (0.53–1.25)	NS
C Cardiovascular system	269 (18.8)	143 (21.5)	126 (16.4)	0.72 (0.55–0.93)	0.0140	0.86 (0.65–1.14)	NS
D Dermatologicals	2 (2.8)	2 (5.1)	0	–	–	–	–
G Genitourinary system and sex hormones	5 (2.5)	4 (4.3)	1 (0.9)	0.21 (0.1–1.89)	NS	0.09 (0.01–1.12)	NS
H Systemic hormonal preparations, excluding sex hormones and insulins	90 (13.9)	51 (13.8)	39 (13.9)	1.01 (0.65–1.59)	NS	1.12 (0.70–1.79)	NS
J Anti-infectives for systemic use	143 (13.8)	69 (15.8)	74 (12.4)	0.76 (0.53–1.08)	NS	0.69 (0.48–1.0)	0.0521
L Antineoplastic and immunomodulating agents	85 (42.9)	42 (46.7)	43 (39.8)	0.76 (0.43–1.33)	NS	0.94 (0.50–1.80)	NS
M Musculoskeletal system	57 (8.8)	44 (12.6)	13 (4.3)	0.31 (0.17–0.60)	0.0004	0.40 (0.21–0.77)	0.0065
N Nervous system	184 (10.7)	101 (13.2)	83 (8.7)	0.62 (0.46–0.84)	0.0023	0.74 (0.53–1.03)	NS
P Antiparasitic products, insecticides and repellents	4 (9.5)	3 (15.0)	1 (4.6)	0.27 (0.03–2.83)	NS	0.33 (0.03–3.96)	NS
R Respiratory system	14 (2.2)	6 (2.1)	8 (2.2)	1.09 (0.37–3.18)	NS	1.37 (0.45–4.23)	NS
S Sensory organs	2 (2.5)	2 (4.1)	0	–	–	–	–
V Various	10 (3.3)	2 (1.7)	8 (4.4)	2.7 (0.56–12.9)	NS	3.58 (0.57–22.45)	NS

NS = Not significant.

¹ The percentage given refers to the overall number of the relevant gender.

drugs (M; n = 434), mainly penicillin (J01, 26.3%), quinolone (J01, 22.2%), ibuprofen (M01, 17.5%) and diclofenac (M01, 19.8%).

For males, no ATC group was significantly prominent as being associated with distinct ADR agents.

Discussion

There has been much debate about the higher ADR risk in females and the higher amount of drug prescriptions in contrast to male patients [11]. However, little is known about gender differences in prescribing different drug classes and their risk of causing ADRs. The aim of this study was to evaluate the diversity of drug prescriptions in male and female patients and to identify gender-specific high-risk drug classes, based on ATC-anatomical first and second levels.

Most authors suggest that females receive more prescriptions because of their higher average age and that they are thus more exposed to polypharmacy. Indeed when adjusted for potential confounding factors like age and the total amount of drugs prescribed, only 4 out of 14 ATC-anatomical groups showed significant gender differences. Three drug classes predominantly affect females, i.e. medications related to blood and blood-forming organs (B), systemic hormonal preparations excluding sex hormones and insulins (H), and the musculoskeletal system (M). They were all significantly more often prescribed in females. In contrast, anti-infectives for systemic use (J) were most often prescribed in males.

With regard to ADRs, in 4 out of 14 ATC anatomical classes, ADRs were more often seen in women. The risk of ADRs was higher in women for drugs of the alimentary tract and metabolism (A), cardiovascular system (C), musculoskeletal system (M) and nervous system (N).

Some investigators demonstrated higher ADR risks for females in psychotropics (N) [18] and antidepressants (N) [19]. In contrast, Rabkin et al. [20] could not find gender-related differences for antidepressants (N). Likewise, we could find a higher ADR risk for females in unadjusted results for prescriptions for the nervous system (N). However, after adjustment no influence remained. In line with other authors [7], a higher ADR risk was identified in women for drugs of the cardiovascular system (C) and alimentary tract and metabolism (A) [12]. However, adjusted for potential confounding factors, no impact was verifiable any more.

Adjusting the analysis for age, for the total amount of drugs prescribed and for each drug class applied (first and second ATC level), a higher ADR risk was still evident for anti-infective (J) and musculoskeletal system (M) prescriptions. In our population, the therapeutic main groups within the above-mentioned drug classes were antibacterials (J) and anti-inflammatory (M) drugs. Our analysis could not identify any anatomical group (ATC) as a risk group for inducing ADRs particularly in males.

In our opinion there are 2 possibilities for these phenomena. The first is that there is really no influence; the second is that the ATC anatomical level summarizes different therapeutic groups which, in terms of their individual active ingredients from a pharmacological point of view, can be so heterogeneous that clear effects of individual active ingredients were statistically lost in the 'interplay of the overall group'.

Due to the small number of patients with regard to therapeutic groups, we were not able to statistically verify these concepts. A larger population would be needed to analyze and confirm these outcomes.

Nevertheless, an analysis based on anatomical main groups (ATC) enables to better focus on particular risk classes for women. Thus, we were able to identify antibiotics from group J as most commonly prescribed, mainly penicillins (J01) and quinolones (J01). Anti-inflammatory drugs dominated in group M, mainly diclofenac (M01) and ibuprofen (M01).

A higher ADR risk in females for anti-infectives (J) has already been suggested in the literature [21]. Interestingly, we could not detect any influence in the risk of anti-infectives (J) for causing ADRs until we adjusted for age, amount of prescriptions and type of drug class.

An increase in ADRs occurring in females due to musculoskeletal system (M) prescriptions was described by Neutel et al. [22] and Figueras et al. [23] (nonsteroidal anti-inflammatory drugs). In this study the risk of developing severe gastrointestinal events increased with the number of NSAID prescriptions and was considerably greater for females than for males. In a stratified analysis by age and gender, it was clear that gender was the greater influence [19]. Interpretation of these results is difficult. In recent years it has become clear that gender differences exist both in pharmacokinetics and pharmacodynamics. Differences in metabolizing enzymes, body composition (body fat and body water content), renal clearance capacity and hormonal differences are considered as responsible factors [24].

The most widely prescribed drugs for the musculoskeletal system, ibuprofen and diclofenac, are metabolized by CYP2C9. No differences exist in the activity of the enzyme between genders [24]. However, in a placebo-controlled, double-blind crossover study of experimental pain, the same dosage of ibuprofen yielded a twofold greater volume of distribution when body weight was taken into consideration. This could explain the more frequent occurrence of ADRs in females [25].

The most often prescribed drug from the anti-infective group, penicillin, has already been described for increased ADR risk. Possibly the decreased activity of the underlying metabolizer P-glycoprotein in females could be responsible for this [24].

The pharmacokinetics of fluoroquinolones like orally administered ciprofloxacin also showed gender-specific variations resulting in a 30% higher maximum concentration in females and a significantly slower oral clearance compared to males [26].

The Food and Drug Administration reviewed 300 new drug applications. Only 163 included a sex analysis. Eleven drugs showed a difference in pharmacokinetics exceeding 40% between males and females [27].

However, if simply dosing females based on their different pharmacokinetics decreases the incidence of ADR remains unclear. To heighten drug safety for females, the complex interaction between pharmacokinetics, pharmacodynamics and pharmacogenetics needs much more research.

To our knowledge our study is the first epidemiological analysis integrating potential confounding factors

such as age and number of prescriptions in a multiple logistic regression model to prove differences in ADRs induced by different drug classes with particular respect to male and female gender.

Conclusion

The results confirm that antibacterials and anti-inflammatory agents are associated with significantly more ADRs in females than in males. Further investigations should focus on these drug classes to identify high-risk therapeutic agents and to understand the potential gender-based mechanism causing these effects.

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