

ORIGINAL ARTICLE

Prescribing of Potentially Inappropriate Medications for the Elderly

An Analysis Based on the PRISCUS List

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SUMMARY

Background: The PRISCUS list of potentially inappropriate medications (PIM) for the elderly was published in 2010 and is the first systematically constructed list of this type in Germany. The aim of the present study is to estimate the baseline prevalence of the prescribing of PIM, as defined by the PRISCUS list.

Methods: Pseudonymized claims data from three statutory health insurances in Germany, which together covered more than 8 million insurants, for the year 2007 were used to determine the age- and sex-standardized one-year period prevalence of PIM among the elderly, as well as the frequency of PIM prescribing per person. The study population included all insurants who were at least 65 years old and were continuously insured throughout the year 2007 or died during that year.

Results: Of the 804 400 elderly persons in the study population, 201 472 (25.0%) received at least one PIM prescription in 2007. The PIM prevalence was higher in women than in men (32.0% vs. 23.3%) and increased with age. The most commonly prescribed PIM were amitriptyline (2.6%), acetyldigoxin (2.4%), tetrazepam (2.0%), and oxazepam (2.0%). 8.8% of all elderly persons received the same PIM drug four or more times in 2007.

Conclusion: These data show that PIM were frequently prescribed to elderly persons in Germany before the PRISCUS list was published. Medications on the PRISCUS list are not necessarily absolutely contraindicated, and this study contained no information about the individual risk/benefit analyses that may have been carried out before these drugs were prescribed; thus, no conclusion can be drawn about the prevalence of inappropriate prescribing. Further research is needed to validate the PRISCUS list, which was generated by expert consensus, as a basis for therapeutic guidelines in geriatric medicine.

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With the prospect of demographic changes in Germany—the number of people over the age of 64 is predicted to increase by about half by the end of 2030 (1)—the question of health care of the elderly is being increasingly highlighted. As people get older, their health problems increase. The range of physical diseases seen in old age is dominated in particular by cardiovascular disease and diseases of the musculoskeletal apparatus (2). Heart failure, stroke, and angina pectoris were the three most common diagnoses for hospital admissions among older people in Germany between 2005 and 2009 (3), while in terms of mental illness, dementia and depression are particularly significant (2).

As patient age goes up, so also does the number of patients with multi-morbidity and polypharmacy, as was shown in the Berlin Age Study and in the Age Survey 2002 for Germany (2). Multi-morbidity and polypharmacy are important predictors of the occurrence of unwanted drug effects and can prolong the hospital stay of older patients (4, 5). However, the sole administration of certain medical drugs can also increase the risk of unwanted drug effects in elderly patients, and for this reason experts have judged them to be potentially inappropriate medications (PIM). In 1997, the first 63 criteria for PIM in older persons were defined for the first time in the USA in the Beers List (e1). This list was updated in 2003 with 66 drugs judged by experts to carry a high risk of unwanted effects (e2). Because of differences in the nature of the market and prescribing practices, other countries such as Canada (e3) and France (e4) developed other PIM lists. In August 2010 the first German PIM list was published, based on a qualitative analysis of international PIM lists and a structured survey of expert opinion. This list, named PRISCUS after the group that carried it out (www.priscus.net), contains 83 PIM drugs in 18 drug classes with recommendations for therapeutic alternatives and other measures for clinical practice (6). The PRISCUS list is not a “list of forbidden substances” in the sense of absolute contraindication, but contains relevant information about the risks of individual drugs for older people, and thus sharpens awareness about the problems that can occur with medical drugs in older people. It does not, however, replace individual risk–benefit assessment, according to which treatment

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TABLE 1

Study population characteristics (N = 804 400)

	Men	Women	All
No. of insurants (%)	447 592 (55.6)	356 808 (44.4)	804 400
Age, mean (SD), years	71.1 (5.5)	72.3 (6.7)	71.6 (6.1)
Age group (years) (%)			
65–69	219 295 (49.0)	160 796 (45.1)	380 091 (47.3)
70–74	123 107 (27.5)	86 391 (24.2)	209 498 (26.0)
75–79	65 800 (14.7)	53 194 (14.9)	118 994 (14.8)
80–84	27 807 (6.2)	34 049 (9.5)	61 856 (7.7)
85–89	8903 (2.0)	14 938 (4.2)	23 841 (3.0)
90–94	2198 (0.5)	5749 (1.6)	7947 (1.0)
≥ 95	482 (0.1)	1691 (0.5)	2173 (0.3)
No. of insurants admitted to hospital in 2007 (%)			
	116 145 (26.0)	86 978 (24.4)	203 123 (25.3)
Morbidity			
Essential hypertension	280 433 (62.7)	222 466 (62.3)	502 899 (62.5)
Chronic ischemic heart disease	114 550 (25.6)	51 577 (14.5)	166 127 (20.7)
Gonarthrosis	63 041 (14.1)	72 545 (20.3)	135 586 (16.7)
Coxarthrosis	44 490 (9.9)	44 679 (12.5)	89 169 (11.1)
Heart failure	43 998 (9.8)	39 526 (11.1)	83 524 (10.1)
No. of drugs^{*1} in 2007, mean (SD)			
	5.6 (4.7)	6.2 (4.8)	5.9 (4.8)

*1 seven-digit ATC code

with a PRISCUS-list drug may still be necessary (e5).

From the societal point of view, the risk of unwanted drug effects that could occur because of a PIM prescription is closely linked to the frequency with which these drugs are prescribed. Analysis carried out by the Scientific Institute of the National Health Insurance Schemes (WiDO, *Wissenschaftliches Institut der AOK*), on the basis of all reimbursable drug prescriptions in the German statutory health insurance (SHI) system in 2009, showed that on average 5.6% of all prescriptions for patients aged 65 or over were for a drug on the PRISCUS list. For patients aged over 90 years, the figure was as high as 6.6% (7). It was likewise reported that in a sample of more than 6 million pieces of anonymized patient data, almost one in three of those aged 65 or over who were insured in the SHI system (29%) had been prescribed at least one drug on the PRISCUS list in 2009 (7). To our knowledge, no other scientific publications exist about the prevalence of older persons with PIM and, especially, about individual PIM drugs and drug classes on the PRISCUS list.

The aim of this study was to estimate the prevalence of PIM for older people on the basis of a large database for Germany according to age, sex, drug, and drug class. The results can then serve as a baseline for future studies once the PRISCUS list comes into general use. The frequency of PIM prescriptions per patient was also evaluated.

Methods

Study design and data sources

In a retrospective epidemiological study, available pseudonymized data from three statutory health insurance companies (AOK Bremen/Bremerhaven, Techniker Krankenkasse, and hkk), with over 8 million insurants throughout Germany, were retrieved from the pharmaco-epidemiological research database of the Bremen Institute for Research on Prevention and Social Medicine (BIPS, *Bremer Institut für Präventionsforschung und Sozialmedizin*) for the period from 1 January 2007 to 31 December 2007 and were analyzed. At the time of the analysis, this was the most recent date for which data from all three insurers were available. The BIPS research database includes, in addition to the patients' core data, all the data relating to reimbursement by the participating insurers for hospital treatment, outpatient treatment under the SHI system, and outpatient medical drug prescriptions. These data were linked via an insurant pseudonym. The drug data contained all prescriptions that were reimbursed by the insurers and fulfilled at pharmacies, coded by a unique *Pharmazentralnummer* (PZN, a nationwide standardized identification number for medicines and pharmaceutical products) for each drug. A reference database of the BIPS was used to identify the prescribed drugs and drug classes from the PZN. This database contains information about the product name, active substance, strength of a single dosage form, package size, anatomical therapeutic chemical classification (ATC code), and the formulation (e.g., immediate or sustained release).

The use of SHI data for scientific research is regulated in Germany by §75 of the Social Security Code (SGB X). The data protection policy developed at BIPS for the research project was approved by the participating health insurers and the relevant federal and state authorities.

Study population

The study population included all insurants who were 65 years or older at the beginning of the period under analysis and were insured throughout 2007 or died in that year.

Potentially inappropriate medications (PIM)

In accordance with the PIM list of the PRISCUS research group, the PIM drugs in the medical drug data were identified by their ATC codes. They were divided into drug classes on the basis of the 3- or 4-digit ATC code. In the case of nifedipine and tolterodine, only the immediate release forms were included in the analysis,

since only these are classified as PIM in the PRISCUS list.

Statistical analysis

The study population was analyzed descriptively according to age, sex, morbidity, and medication. Morbidity was investigated on the basis of outpatient and inpatient diagnoses (ICD-10 codes) that, according to hospital statistics, most commonly necessitated hospital admission in women and men aged 65 years or older (*eTable 1*) (3). The presence of at least one confirmed outpatient diagnosis or an inpatient primary or secondary diagnosis was counted as disease.

Categoric variables were described by their absolute and relative frequency, numeric variables by their mean and standard deviation (SD). To estimate the 1-year period prevalence of PIM (PIM prevalence), the relationship between the insurants who had received at least one PIM during 2007 and the study population as a whole was determined. The prevalence calculation was done once for all PIMs, and separately for each drug class and each drug, in each case stratified according to age and sex. In order to be able to make representative statements according to age and sex, the results were standardized according to the age and sex distribution of the German population as on 31 December 2007 (8).

To evaluate the prevalence of PIM prescriptions, the number of PIM prescriptions with the same and with different PIM drugs per person was determined. All analyses were carried out in SAS (version 9.2, SAS Institute Inc., Cary, NC).

Results

Characteristics of the study population

More than 804 400 insurants aged 65 years and over were included in the study: 447 592 men (55.6%) and 356 808 women (44.4%). Out of these, 20 340 died during 2007. The mean age of the study population was 71.6 years (SD: 6.1). *Table 1* shows the distribution of the insurants according to sex, age group, and clinical characteristics such as hospital stays, morbidity (five most frequent diagnoses), and medication. The mean number of different drugs was 6.2 (SD: 4.8) for women and 5.6 (SD: 4.7) for men. A quarter of these older people (25.3%) received inpatient treatment in hospital.

Prevalence of PIM

The authors identified 201 472 older people (25.0%) who received at least one PIM prescription during 2007, 96 552 of them men (21.6%) and 104 920 of them women (29.4%). After standardization for age and sex, the prevalence of PIM was 28.3%. The age-standardized prevalence was greater for women (32.0%) than for men (23.3%). Psycholeptics (neuroleptics, benzodiazepines, Z-drugs such as zolpidem, zopiclone, and zaleplon and other sedatives) had the highest prevalence (10.9%), followed by the psychoanaleptics (antidepressants and piracetam) (6.6%), antiphlogistics/antirheumatics (3.4%), and cardiac drugs (3.3%)

TABLE 2

Prevalence of PIM according to drug class and sex

Drug class (ATC code)	Prevalence in % (per 100 insurants)		
	All* ¹	Men* ²	Women* ²
Psycholeptics (N05)	10.92	7.14	13.66
Psychoanaleptics (N06)	6.56	3.88	8.51
Antiphlogistics/antirheumatics (M01)	3.40	2.75	3.87
Cardiac therapy (C01)	3.33	2.84	3.70
Muscle relaxants (M03)	2.28	1.95	2.52
Urologics (G04)	2.16	2.80	1.70
Antihypertensives (C02)	2.05	2.62	1.63
Peripheral vasodilators (C04)	1.61	1.66	1.58
Beta-blocking agents (C07)	1.12	1.19	1.07
Calcium channel blockers (C08)	1.17	0.97	1.31
Antibiotics (J01)	1.00	0.55	1.32
Antihistamines (R06)	0.28	0.25	0.30
Ergotamine derivatives (N02C, N04)	0.13	0.10	0.15
Antiemetics (A04)	0.12	0.09	0.14
Antithrombotics (B01)	0.10	0.13	0.08
Antiepileptics (N03)	0.02	0.02	0.02
Opioids (N02A)	0.01	0.01	0.01
Laxatives (A06)	0.01	0.01	0.01

*¹ standardized prevalence according to age and sex
*² standardized prevalence according to age

(*Table 2*). Most of the 18 drug classes also showed higher prevalence among women than among men; the exceptions were urologics (2.8% men, 1.7% women), antihypertensives (2.6% men, 1.6% women), beta-blockers (1.2% men, 1.1% women), and antithrombotics (0.13% men, 0.08% women) (*Table 2*). The prevalence of PIM increased with age from 20.3% in the group of 65- to 69-year-olds to a maximum of 42.0% among the 90- to 94-year-olds (*Figure*).

With the exception of three drugs (prasugrel, triprolidine, and chlorphenamine), all drugs on the PRISCUS list were prescribed for older people in 2007. Those with a prevalence of 1% or more are listed in *Table 3*. The complete list of all PIM drug prevalences is available in *eTable 2*.

Assessment of the frequency of PIM per patient

Seventy-four percent of all insurants prescribed a PIM had only one PIM drug prescribed; 19% had two, and 5.1% and 1.4% respectively had three or four different PIM drugs prescribed during 2007.

70 550 insurants (35.0% of insurants with PIM, or 8.8% of all insurants) received four or more PIM prescriptions for the same PIM drug in 2007. A total of 78

TABLE 3

Prevalence of PIM according to drug and sex

Drug	Prevalence per 1000 insurants		
	All* ¹	Men* ²	Women* ²
Amitriptyline	25.95	13.07	35.30
Acetyldigoxin	24.29	20.72	26.88
Tetrazepam	20.21	16.92	22.60
Oxazepam	19.70	10.81	26.15
Zopiclone	17.18	12.09	20.87
Bromazepam	16.64	9.58	21.76
Doxepin	16.01	8.13	21.73
Diazepam	13.30	9.64	15.96
Lorazepam	13.28	8.57	16.70
Zolpidem	12.94	9.17	15.67
Doxazosin	12.78	21.39	6.54
Nifedipine ^{†3}	11.40	9.22	12.98
Etoricoxib	11.33	8.91	13.08
Sotalol	11.22	11.92	10.70
Trimipramine	10.94	5.68	14.75
Pentoxifylline	10.73	11.58	10.11
Nitrofurantoin	9.95	5.51	13.17

*¹ standardized prevalence according to age and sex
 *² standardized prevalence according to age
 *³ exclusively immediate release formulations

drugs (94% of all PIM drugs) were identified; the 40 most frequent are shown in *Table 4*.

Discussion

The present study provides extensive information about the current status regarding the prescription of potentially risky medical drugs in elderly people in Germany. With the exception of three drugs—prasugrel, triprolidine, and chlorphenamine—all drugs on the PRISCUS list were prescribed in the present study in 2007. The thrombocyte aggregation inhibitor prasugrel has been marketed in Germany since April 2009, and for that reason could not be included in this analysis. Triprolidine and chlorphenamine are first-generation antihistamines that are mainly sold over the counter in combination preparations for self-medication of colds and flu.

After standardization for age and sex distribution in Germany, over a quarter (28.3%) of the older people received at least one PIM prescription in 2007. This finding agrees with results of similarly designed German studies based on either the PRISCUS list (7, 9, 10) or on an international PIM list (11). Review articles of studies in Europe and the USA report PIM prevalences

of 12% or more in the outpatient setting and up to 40% in care homes (12, 13). The drug class that includes the psycholeptics—at a total of 31 drugs, the largest class in the PRISCUS list—showed the highest prevalence. Frequently prescribed drugs in this class were the long-acting benzodiazepines bromazepam and diazepam, the short- and medium-acting benzodiazepines oxazepam and lorazepam, and the Z-drugs zopiclone and zolpidem. In older people, an increased risk of fall, hip fracture, injury, and psychiatric and paradoxical reactions has been reported in association with taking these drugs (6). In the present study these drugs were also identified as being prescribed several times for one patient. According to the package information leaflet, the treatment duration should be a maximum of 4 weeks, irrespective of age, because the use of benzodiazepines or benzodiazepine-like drugs can lead to the development of psychological and physical dependence. Various studies have reported that older people were often taking these substances for longer than the recommended duration of treatment (12, 14), as is also suggested by the present study.

The high prevalence of prescriptions for benzodiazepines and tricyclic antidepressants such as amitriptyline, doxepin, and trimipramine has been previously described in other national studies, particularly in older patients with generalized anxiety disorder (15), those living in care homes (11), and those being cared for in their own homes (16), as well as in international studies (13, 17, 18). The same is true for the results of our study with regard to nifedipine, acetyldigoxin and other digitalis glycosides (with the exception of digitoxin, which is not characterized as a PIM in the PRISCUS list), doxazosin, etoricoxib, sotalol, pentoxifylline, nitrofurantoin, and clonidine (7, 9, 19–21). It should be noted that the assessment of antidepressants in the PRISCUS list focused on depression as the indication (e5); however, amitriptyline is regarded as appropriate even in older people when given at a low dose for neuropathic pain (22, e6). Reserpine, one of the oldest antihypertensives, whose role continues to be debated against the background of adverse effects such as depression and sedation (23), showed a prevalence of 0.4%.

The cited prevalence of nifedipine and tolterodine refers exclusively to the immediate release drugs, since only these are classified as PIMs in the PRISCUS list. A subgroup analysis showed that more than half of all prescriptions of nifedipine and tolterodine related to sustained release preparations, which, because of the slow release of drug, do not appear to be associated with an increased risk of myocardial infarction or increased mortality in older people. For digitalis glycosides, which are associated with increased risk of intoxication and falls (6), a detailed analysis taking into account indications, co-medications, and daily dose appears desirable, in order to take into account the recommendations of the current treatment guidelines. For example, digoxin is recommended in the treatment of atrial fibrillation with rate control, but in patients with

systolic cardiac failure and sinus rhythm (25) it is described as a reserve drug.

So far as we know, repeated prescription of the same PIM has not been investigated before. Our study shows that a large number of the drugs on the PRISCUS list were prescribed four or more times in 8.8% of all older people, which is an indication of long-term treatment. At the same time, this could be interpreted as an indication that these patients were able to tolerate this PIM therapy.

Limitations

This study was a descriptive analysis. Factors that could have a significant influence on PIM prescription, such as sex, age, living in a care home, the specialty of the prescribing physician, or the financial situation or care level of the patient, were not investigated because for various of these factors (financial situation, care home, care level) no information was available.

For nine drugs from the benzodiazepine, neuroleptic, and Z-drug subgroups, the PRISCUS list gives upper dose limits beyond which they are to be rated as PIM. Because the secondary data contain no information about individually prescribed daily doses, the PIM prevalence may have been overestimated for these drugs. A sensitivity analysis excluding these dose-dependent drugs resulted in a PIM prevalence for the psycholeptics (5.1%) that was reduced by half, but the overall PIM prevalence only dropped from 28.3% to 24.6%.

The study did not allow us to estimate the number of inappropriate prescriptions, since the contraindication in relation to drugs on the PRISCUS list is only relative, and the present authors had no information about how benefits were weighed against risks in the individual prescriptions for these drugs.

The study population was younger overall than the overall population of Germany in 2007, and had a larger proportion of men over the age of 65 years (55.6% in the study population versus 42% in the overall population). To ensure that we could calculate representative prevalences according to age and sex, therefore, we standardized our data for the German population in 2007. The study was based on prescriptions handed in at pharmacies. The data contain no information about whether the patients actually took the prescribed drugs. Poor patient compliance would mean that PIM prevalences and the associated potential risks were overestimated. To take at least some account of the important element of compliance and persistence of the dispensed medicine, the frequency of PIM per patient was analyzed.

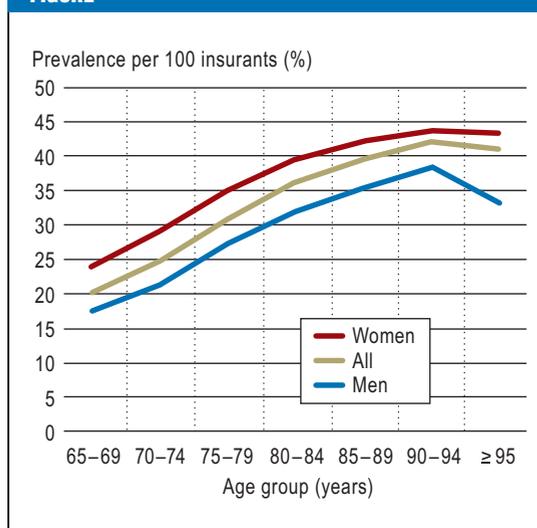
The results of our study show that, before the PRISCUS list was published, the medications it included as potentially inappropriate were prescribed to older people on a considerable scale. Further research is needed to analyze the clinical relevance of the drugs on the PRISCUS list in terms of the risk of complications of therapy in comparison to those of alternative treatments.

TABLE 4

Potentially inappropriate drugs prescribed four or more times for the same person

Drug	No. of insurants	Drug	No. of insurants
Acetyldigoxin	5868	Oxybutynin	1332
Amitriptyline	4777	Baclofen	1247
Sotalol	4688	Metildigoxin	1242
Doxazosin	4216	Reserpine	1096
Zopiclone	4010	Tetrazepam	1019
Oxazepam	3737	Temazepam	932
Doxepin	3641	Olanzapine	847
Zolpidem	3459	Solifenacin	790
Lorazepam	2874	Indometacin	756
Bromazepam	2747	Etoricoxib	746
Terazosin	2115	Flunitrazepam	698
Piracetam	2056	Acemetacin	672
Flecainide	1921	Nitrofurantoin	636
Pentoxifylline	1831	Piroxicam	563
Trimipramine	1815	Haloperidol	558
Clonidine	1756	Flurazepam	549
Naftidrofuryl	1738	Fluoxetine	523
Diazepam	1533	Meloxicam	510
Nifedipine	1522	Nitrazepam	493
Lormetazepam	1380	Tolterodine	492

FIGURE



One-year period prevalence of PIM according to age group and sex in 2007

KEY MESSAGES

- At 28.3%, the prevalence of prescriptions of potentially inappropriate medications (PIMs) on the PRISCUS list is substantial.
- Women have PIMs prescribed more often than men do.
- Among PIM drugs, the benzodiazepines, neuroleptics, sedatives, antidepressants, and digitalis glycosides are the most frequently prescribed.
- 8.8% of older people were prescribed the same PIM four or more times in 2007.
- There is a need for further research, especially into the clinical relevance of the substances in the PRISCUS list in terms of the risk of complications of therapy in comparison to alternative therapies.

Conflict of interest statement

Ute Amann is on the advisory board of Vetter Pharma-Fertigung GmbH & Co.Kg.

Professor Garbe has received honoraria from NYCOMED, is a consultant for Bayer-Schering and Novartis, has received honoraria for expert opinions from Bayer AG, has received reimbursement of costs from Sanofi Pasteur, Bayer-Schering, Boehringer Ingelheim, and Pfizer, and has received funds into a third-party account from Bayer-Schering AG.

Niklas Schmedt declares that he has no conflict of interests.

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ORIGINAL ARTICLE

Prescribing of Potentially Inappropriate Medications for the Elderly

An Analysis Based on the PRISCUS List

Ute Amann, Niklas Schmedt, Edeltraut Garbe

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eTABLE 1

Most common diagnoses among men and women aged over 65 years who were discharged from hospital (source: German hospital statistics base year 2009 [3])

Diagnosis	ICD-10
Heart failure	I50
Cerebral infarction	I63
Angina pectoris	I20
Atrial fibrillation and flutter	I48
Pneumonia, organism unspecified	J18
Acute myocardial infarction	I21
Gonarthrosis (arthrosis of knee)	M17
Other chronic obstructive pulmonary disease	J44
Fracture of femur	S72
Essential (primary) hypertension	I10
Chronic ischemic heart disease	I25
Malignant neoplasm of bronchus and lung	C34
Atherosclerosis	I70
Coxarthrosis (arthrosis of hip)	M16
Malignant neoplasm of breast	C50

eTABLE 2

Prevalence of PIM according to drug and sex per 1000 insureds

	PIM drug	All ^{*1}	Men ^{*2}	Women ^{*2}
1	Amitriptyline	25.95	13.07	35.30
2	Acetyldigoxin	24.29	20.72	26.88
3	Tetrazepam	20.21	16.92	22.60
4	Oxazepam	19.70	10.81	26.15
5	Zopiclone	17.18	12.09	20.87
6	Bromazepam	16.64	9.58	21.76
7	Doxepin	16.01	8.13	21.73
8	Diazepam	13.30	9.64	15.96
9	Lorazepam	13.28	8.57	16.70
10	Zolpidem	12.94	9.17	15.67
11	Doxazosin	12.78	21.39	6.54
12	Nifedipine ^{*3}	11.40	9.22	12.98
13	Etoricoxib	11.33	8.91	13.08
14	Sotalol	11.22	11.92	10.70
15	Trimipramine	10.94	5.68	14.75
16	Pentoxifylline	10.73	11.58	10.11
17	Nitrofurantoin	9.95	5.51	13.17
18	Oxybutynin ^{*4}	7.90	6.49	8.92
19	Piracetam	7.88	8.46	7.46
20	Piroxicam	7.01	5.49	8.12
21	Meloxicam	6.04	4.23	7.35
22	Naftidrofuryl	5.80	5.41	6.09
23	Terazosin	5.55	12.92	0.20
24	Indometacin	5.20	5.28	5.15
25	Lormetazepam	5.10	3.26	6.43
26	Metildigoxin	4.89	3.18	6.12
27	Haloperidol	4.86	3.64	5.75
28	Solifenacin	4.82	3.68	5.64
29	Acemetacin	4.33	3.22	5.14
30	Clonidine	4.06	3.65	4.36
31	Reserpine	3.93	2.31	5.11
32	Flecainide	3.70	4.05	3.44
33	Temazepam	3.59	2.35	4.50
34	Baclofen	2.75	2.77	2.74
35	Fluoxetine	2.48	1.44	3.24
36	Hydroxyzine	2.38	1.76	2.82
37	Flunitrazepam	2.34	1.69	2.82
38	Tolterodine ^{*3}	2.28	1.46	2.88
39	Ergotamine	2.06	1.41	2.53
40	Flurazepam	2.06	1.28	2.63
41	Nitrazepam	2.01	1.32	2.51
42	Alprazolam	1.85	1.17	2.35
43	Clorazepate dipotassium	1.82	1.26	2.24

44	Maprotiline	1.80	0.67	2.62
45	Olanzapine	1.78	1.17	2.22
46	Chloral hydrate	1.62	1.22	1.91
47	Dimetindene	1.56	1.40	1.67
48	Clomipramine	1.54	0.82	2.06
49	Brotizolam	1.49	1.08	1.79
50	Levomepromazine	1.45	1.11	1.70
51	Nicergoline	1.28	1.22	1.33
52	Dimenhydrinate	1.16	0.84	1.39
53	Dihydroergotoxin	1.12	0.78	1.37
54	Medazepam	1.09	0.77	1.32
55	Clemastine	1.04	0.95	1.10
56	Ticlopidine	0.99	1.30	0.76
57	Ketoprofen	0.95	0.77	1.09
58	Digoxin	0.90	0.81	0.96
59	Clobazam	0.84	0.67	0.96
60	Clozapine	0.84	0.91	0.79
61	Triazolam	0.72	0.51	0.87
62	Prazepam	0.67	0.45	0.84
63	Phenylbutazone	0.64	0.68	0.60
64	Imipramine	0.57	0.40	0.69
65	Chlordiazepoxide	0.56	0.29	0.75
66	Thioridazine	0.47	0.23	0.65
67	Prazosin	0.42	0.48	0.37
68	Quinidine	0.32	0.49	0.20
69	Perphenazine	0.30	0.10	0.44
70	Dihydroergo-cryptin mesilate	0.26	0.33	0.20
71	Methyldopa	0.24	0.17	0.28
72	Fluphenazine	0.22	0.12	0.29
73	Phenobarbital	0.22	0.23	0.21
74	Tranlycypromine	0.18	0.10	0.23
75	Zaleplon	0.17	0.14	0.19
76	Pethidine	0.13	0.13	0.13
77	Viscous paraffin	0.10	0.10	0.10
78	Diphenhydramine	0.03	0.03	0.02
79	Doxylamine	0.02	0.00	0.03

*¹ standardized prevalence according to age and sex

*² standardized prevalence according to age

*³ exclusively immediate release formulations

*⁴ oxybutynin immediate release and sustained release (listed as separate PIM drugs in the PRISCUS list) were taken together