Original Article

Problematic Medication With Benzodiazepines, “Z-drugs”, and Opioid Analgesics

An Analysis of National Health Insurance prescription data from 2006–2016

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Summary

Background: An estimated 1.4 to 2.6 million people in Germany suffer from drug dependence. Most of them are long-term users of benzodiazepines (BZD), Z drugs (ZD), or opioid analgesics (OA).

Methods: This analysis is based on prescription data from patients of the national statutory health insurance system in the German federal states of Schleswig-Holstein, Hamburg, Bremen, and Lower Saxony. Drug-taking trends, duration, dosage, and long-term use of BZD, ZD, and OA in the years 2006 to 2015 are analyzed; prevalences are estimated for the years 2006 to 2016.

Results: In 2006, 7.7% of patients received at least one prescription for a BZD, ZD, or OA; in 2016, 7.0% did. Over the period of analysis, a marked drop was seen in prescriptions of BZD and a slight fall in prescriptions of ZD (2006: BZD 3.5%, ZS 1.1%; 2016: BZD 2.0%, ZS 0.8%), but there was also an increase in prescriptions of OA, from 4.2% to 4.9%. The number of defined daily doses (DDD) prescribed per year fell for both BZD and ZD. For OA, the number of DDD prescribed per year rose from 2006 to 2009 and decreased by a small amount in subsequent years. The proportions of BZD and ZD patients who had long-term prescriptions fell over time, while the corresponding percentage of OA patients rose.

Conclusion: Nearly one-fifth of all prescriptions for BZD were long-term prescriptions for an entire year, in violation of the relevant guidelines. The rising prevalence of OA use was in the expected range in view of the aging population, but the number of prescriptions rose among younger patients as well. This trend toward more common treatment with opioid analgesics should be critically examined.

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Besides their intended effects, medicines often have unwanted side effects, including the development of prescription drug misuse, potentially leading to dependence. In Germany, an estimated 1.4 to 2.6 million people are dependent on prescription drugs (1–3), primarily sleeping drugs and tranquilizers (benzodiazepines [BZD] or Z-drugs [ZD]) or opioid analgesics (OA). According to a study by Buth et al. (4), 5.1% of the German population were taking BZD (including tetrazepam) and a further 1.1% one of the so-called Z-drugs in 2010. These rates were significantly higher among female patients and especially the elderly. Based on a 3-year period (2006 to 2008), 16.7% of patients who were prescribed BZD and/or ZD were found to show a problematic pattern of use (5). The majority were elderly patients taking the drugs in low doses over very long periods of time. This so-called low-dose dependence can have significant adverse effects on the health of these patients; for instance, it often leads to fractures (6, 7), pneumonia (8), or dementia (9).

OA are indispensable for the treatment of severe pain and in palliative care. However, there is a risk of patients developing opioid dependence (10). In the United States and Canada, physicians have prescribed OA in large quantities over prolonged periods of time for less severe or temporary pain. Many patients developed OA dependence and later switched to more potent analgesics or to heroin (11).

Similarly, the amounts of OA prescribed in Germany increased by 21% between 2007 and 2016 (12). According to a study by Schubert et al. (13), 4.5% of all patients covered by statutory health insurance (*Gesetzliche Krankenversicherung*, GKV) received an OA (excluding codeine-containing preparations) in 2010. Ten years earlier, the prevalence had been only 3.3% (13). Even though, apart from cancer care, there are few indications for the long-term prescription of OA (14, 15), prolonged treatment with these drugs is common (13, 16).

The aim of this paper is to describe trends in the prescription of BZD, ZD, and OA among the GKV-insured population during the years 2006 to 2016—by sex and age—and to investigate how frequently whole-year prescriptions for these medications were issued.

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FIGURE 1

Prevalence of prescription of medications with dependence potential in the years from 2006 to 2016

Methods

The analyses reported here are based on the prescriptions issued to GKV patients and filled in pharmacies in the German federal states of Schleswig-Holstein, Hamburg, Bremen, and Lower Saxony during the years 2006 to 2016. Data extraction was performed at the North German Pharmacy Data Center (NARZ/AVN), where 65% to 91% of the pharmacies of these states have their prescriptions processed for billing with the statutory health insurers.

In the analyses, these variations in coverage rates were corrected using weighting. The resulting (weighted) case numbers were then related to the total number of persons insured in these states (around 11 million) (17).

The Anatomical Therapeutic Chemical (ATC) classification system of the World Health Organization (WHO) was used to allocate the active ingredients of the prescribed medicines to the three substance groups evaluated in this paper (18). The ATC index applicable in Germany also includes information about the defined daily doses (DDD) assuming the medications are used as intended. Based on the DDD, the prescribed amounts of active substance per patient and patient year (the 12-month period from the first prescription within a calendar year; see *eMethods*) can

be calculated in standardized form, i.e. without the complex and error-prone calculation of equivalent doses (e.g., diazepam or morphine equivalents).

Within the dataset, each prescription was linked to an individual using a unique, anonymized patient code which does not allow tracing of the patient. The statistical software package SPSS, version 25, was used for weighting and descriptive data analysis (19). Given the high case numbers, confidence intervals were not calculated.

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Results

Prevalence of prescription of medications with dependence potential

In the course of the year 2006, 7.7% of the GKV-insured persons received at least one prescription for a BZD, ZD, or OA (including multiple prescriptions). In 2016, this proportion had declined to 7.0%. Looking at the individual substance groups, the reduction in the prevalence of BZD from 3.5% in 2006 to 2.0% in 2016 is striking (*Figure 1*). While the proportion of

TABLE 1

Prevalence of prescriptions of the most important benzodiazepines, Z-drugs, and opioid analgesics by year

		2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Benzodiazepines (BZD)	Lorazepam	17.1%	19.1%	21.0%	23.3%	26.5%	28.8%	31.8%	33.9%	36.2%	38.8%	41.0%
	Diazepam	24.4%	24.4%	24.1%	23.5%	23.3%	22.9%	22.1%	23.3%	24.2%	22.9%	22.3%
	Oxazepam	19.9%	19.3%	18.8%	18.2%	17.0%	16.3%	15.5%	14.3%	13.5%	12.7%	11.7%
	Bromazepam	18.2%	17.8%	17.4%	16.7%	15.7%	15.1%	14.3%	13.4%	12.6%	12.1%	11.4%
	Lormetazepam	5.8%	5.4%	5.3%	4.9%	4.5%	4.2%	4.0%	3.7%	3.4%	3.1%	2.9%
	Other BZD	23.9%	23.0%	22.4%	22.0%	21.2%	20.6%	19.8%	18.8%	17.5%	17.8%	17.9%
	Total BZD patients	390 043	364 169	358 461	334 743	307 940	293 771	278 745	268 726	259 427	247 817	233 637
Z-drugs	Zopiclone	58.7%	60.2%	62.3%	63.2%	64.5%	65.4%	65.4%	66.2%	66.6%	67.4%	68.6%
	Zolpidem	43.5%	41.9%	39.9%	38.8%	37.6%	36.9%	36.7%	35.8%	35.2%	34.5%	33.4%
	Total Z-drug patients	118 088	115 123	122 810	121 459	114 349	115 639	110 897	107 250	104 202	100 203	95 151
Opioid analgesics (OA)	Tramadol	57.5%	57.0%	55.3%	52.9%	50.0%	47.4%	43.6%	44.2%	41.7%	39.3%	37.3%
	Tilidine	21.8%	22.6%	24.1%	25.6%	27.0%	28.7%	30.6%	28.7%	30.6%	31.9%	33.3%
	Oxycodone	6.5%	5.5%	5.3%	5.4%	6.8%	7.3%	7.7%	7.8%	8.9%	10.0%	10.9%
	Oxycodone & naloxone	0.7%	2.8%	3.9%	5.3%	5.6%	5.9%	6.5%	7.6%	8.0%	7.7%	7.4%
	Fentanyl	14.9%	13.8%	13.4%	13.1%	12.8%	12.3%	12.0%	11.7%	11.0%	10.7%	10.4%
	Morphine	9.6%	9.5%	9.3%	9.0%	8.7%	8.4%	8.4%	8.3%	7.9%	7.8%	7.7%
	Hydromorphone	2.4%	2.8%	3.3%	3.7%	4.0%	4.1%	4.1%	4.3%	4.6%	4.8%	5.1%
	Other OA	4.6%	4.9%	4.6%	4.4%	4.3%	5.3%	5.6%	6.0%	6.4%	6.6%	6.7%
	WHO step 2	76.3%	76.5%	76.2%	75.5%	73.8%	72.9%	71.4%	70.1%	69.4%	68.5%	67.7%
	WHO step 3	31.8%	32.1%	32.5%	33.5%	34.8%	35.8%	36.9%	38.2%	39.0%	39.8%	40.5%
	Total OA patients	466 609	474 521	485 631	486 958	496 798	506 806	530 549	524 106	540 303	549 658	560 920

Percentages express the proportion of persons who received a specific active substance in the given year, in relation to all patients of the respective substance group (benzodiazepines, Z-drugs, opioid analgesics). Prescriptions of different active substances within a calendar year per patient are possible. For example: Of the 390 043 BZD patients in 2006, 17.1% received medications containing the active ingredient lorazepam.

patients receiving a ZD also decreased slightly, an increase in patients receiving an OA was noted, from 4.2% in the first to 4.9% in the last year of the study. The proportion of patients receiving a prescription of the BZD lorazepam more than doubled between 2006 and 2016, while the proportion of diazepam prescriptions hardly changed and the proportions of oxazepam and bromazepam prescriptions decreased. In 2016, slightly more than two thirds of the ZD patients were prescribed zopiclone, an increase of 10 percentage points compared with 2006. The proportion of zolpidem prescriptions decreased by the same amount during this period. With regard to the WHO step-2 OA, a significant fall in the proportion of tramadol patients was noted, while tilidine prescriptions rose continuously over the years. As for WHO step-3 analgesics, the development of oxycodone prescriptions is striking: the number more than doubled during the analysis period.

In 2006, 4.6% of the female GKV-insured patients but less than half as many of the men, only 2.2%, received BZD (*eTable 1*).

Likewise, ZD were prescribed around twice as often to women as to men.

A trend towards a slight reduction in prevalence during the study period can be discerned for both ZD and BZD.

The proportion of patients with OA prescriptions was also higher among women—about 1 in 20—than men. During the period covered by our analyses, a slight increase in prevalence of 0.7 percentage points was observed for both sexes.

Furthermore, *eTable 1* shows that prevalence rates continuously increased with advancing age. For example, in 2006 only 0.6% of the 29-year-olds but 11.8% of the 75+ age group received a BZD prescription. At the same time, the reported decrease in prevalence is attributable predominantly to a change in the prescription pattern for the elderly. For ZD, a

FIGURE 2

Dose (DDD) of prescriptions of medications with dependence potential per patient year in the years from 2006 to 2015

similar trend is noted; however, the prevalence rates are lower and the changes during the study period less pronounced than for BZD.

The most noticeable differences among the analyzed age groups were found for OA. For example, in 2006 only 2.0% of the 30- to 44-year-olds were prescribed OA, but 15.4% of those 75 and older. A slight increase is noted in all age groups in the following years.

Amounts of medications prescribed (DDD) and prescription duration

Figure 2 shows the quantity of drugs prescribed per patient year, based on DDD. For both BZD and ZD, a significant reduction is noted. However, this is due solely to a decrease in prescription duration over the years. For example, the average duration of ZD prescriptions declined from 129 days in 2006 to 109 days in 2015. A comparable reduction was observed for BZD. However, the average daily dose prescribed during the prescription period did not change and was approximately 0.7 DDD for both groups.

The continuous reduction in prescribed doses and prescription duration occurred to the same extent in both men and women (Table 2). The absolute values for both sexes exceed the values for the total group, because sex was not stated for all participants (between 88% and 95% per year; for further details see the Limitations section and the eMethods). The decreases in prescription duration and prescribed dose are most pronounced in elderly patients. In the

75+ age group, the average duration of BZD prescription went down by about 38 days and the average prescribed amount of BZD declined by 28 DDD. Notably, the decreases were smaller (–16 days and –15 DDD) among 45- to 59-year-olds. These differences were less pronounced for ZD.

In the BZD group, the average prescribed daily amount of active substance decreased with increasing age. For example, while the 30- to 44-year-olds were prescribed 0.9 DDD on average, the 60- to 74-year-olds were prescribed 0.7 DDD and the oldest patients even less, 0.6 DDD. In contrast, no such age-related differences were found for ZD.

Among the OA patients, the prescribed daily doses showed a steady slight increase between 2006 and 2009, followed by a continuous decrease (Table 2). However, prescription duration increased from 128 days in 2006 to 141 days in 2015. Consequently, the average prescribed amount of medicine varies between 0.7 DDD and 0.8 DDD per day, depending on the observation year.

These trends in OA prescription differed hardly at between male and female patients or among age groups. However, lower amounts of medicine were prescribed to the oldest patients (mean daily dose 0.6 to –0.7 DDD) than, for example, to the 30- to 44-year-olds (mean 0.9 DDD).

Long-term prescriptions

Figure 3 shows the proportion of patients who were prescribed a drug belonging to the respective active

TABLE 2

Duration of the prescriptions (in days) and dose (in DDD) of medications with dependence potential during the years from 2006 to 2015 by sex and age group

		Sex				Age (years)									
		Male		Female		≤ 29		30–44		45–59		60–74		≥ 75	
		Days	DDD	Days	DDD	Days	DDD	Days	DDD	Days	DDD	Days	DDD	Days	DDD
Benzodiazepines	2006	135.7	110.4	137.0	94.9	48.6	42.7	82.1	80.2	108.5	91.4	134.1	97.6	162.2	102.6
	2007	124.1	99.7	128.4	88.4	47.6	40.4	80.4	76.8	105.9	88.6	133.0	95.5	160.1	100.5
	2008	123.1	97.9	125.9	86.5	46.8	39.5	79.3	74.1	104.6	87.4	131.8	94.4	158.0	99.0
	2009	116.6	92.8	119.0	82.0	45.3	37.5	78.0	72.4	101.1	85.0	124.9	89.8	147.9	92.4
	2010	116.0	91.6	116.6	79.7	47.4	38.4	76.8	70.8	99.4	83.3	123.5	88.1	145.8	90.0
	2011	113.8	89.3	113.1	77.6	44.6	35.9	75.4	69.5	97.3	81.4	120.9	86.4	141.0	87.1
	2012	110.7	87.0	109.6	75.2	45.6	35.3	76.0	69.8	95.7	80.1	117.6	84.8	133.6	82.3
	2013	106.5	83.2	107.3	73.0	42.5	32.3	73.5	66.1	93.5	78.0	116.5	83.6	131.0	79.8
	2014	104.1	80.5	104.0	70.6	44.9	33.9	70.0	61.8	90.7	74.8	114.6	82.2	127.3	77.3
	2015	103.7	80.6	103.2	70.2	45.6	34.2	72.8	64.9	92.1	76.6	113.4	81.6	123.6	74.8
Z-drugs	2006	132.3	92.8	140.7	93.7	50.8	38.1	79.7	58.5	112.5	77.7	143.1	95.1	161.0	108.4
	2007	123.6	86.6	135.6	89.8	53.0	37.8	79.3	57.2	109.0	74.1	144.0	95.6	161.7	108.4
	2008	121.7	85.2	134.4	88.8	51.2	36.9	77.2	54.9	108.1	73.0	142.4	94.6	162.9	109.2
	2009	114.3	80.1	124.4	83.2	47.7	34.4	73.7	53.0	99.6	68.4	133.3	89.1	151.1	102.1
	2010	112.6	78.7	122.4	81.6	47.4	34.6	72.4	52.1	97.1	66.7	132.3	88.0	150.6	101.1
	2011	109.2	76.7	118.9	79.1	45.6	33.7	69.6	49.8	93.8	64.2	128.6	85.5	146.5	98.8
	2012	106.9	74.4	114.9	76.4	43.3	32.0	69.9	49.9	91.4	62.1	124.5	82.6	140.0	94.2
	2013	106.2	73.6	114.6	75.7	42.0	31.2	71.2	51.4	89.9	60.7	123.3	81.8	140.8	93.5
	2014	104.5	72.2	113.8	74.8	42.5	30.6	71.2	51.0	90.2	60.4	120.8	79.9	139.4	92.2
	2015	105.2	73.1	112.8	74.1	42.8	31.1	73.4	52.1	91.1	61.6	120.2	79.8	135.3	89.3
Opioid analgesics	2006	136.1	117.9	148.1	109.8	41.1	35.0	81.3	78.4	116.7	106.5	135.4	108.1	152.0	103.9
	2007	125.9	108.9	143.1	107.2	42.2	36.1	80.7	76.5	116.3	105.6	137.1	110.0	155.8	107.4
	2008	128.0	110.6	146.2	109.6	42.7	37.1	82.0	77.7	119.8	108.4	140.9	113.2	161.9	111.7
	2009	129.2	111.4	148.6	110.9	43.3	37.1	83.0	78.1	121.0	110.0	143.7	115.8	165.7	113.3
	2010	129.6	109.9	149.4	110.2	43.4	36.5	84.0	77.2	120.3	107.9	143.9	115.1	167.0	112.8
	2011	131.4	109.5	151.5	110.1	44.4	37.3	85.6	77.1	120.9	107.0	145.6	114.4	169.6	113.4
	2012	130.2	108.1	149.8	108.0	44.4	38.1	84.6	76.0	119.4	105.5	145.0	113.8	166.5	110.1
	2013	132.7	107.8	153.5	108.3	45.2	37.5	84.2	73.3	121.7	105.5	148.8	114.8	170.5	110.4
	2014	132.2	105.6	153.1	106.7	45.6	36.9	82.3	70.8	120.3	103.1	148.5	113.8	171.6	109.4
	2015	132.7	105.2	153.4	105.4	46.3	37.2	82.3	71.6	121.2	102.7	147.9	112.6	171.4	107.8

Between 5% and 12% of patients, depending on the year, could not be included in the sex-specific analyses because their sex was not known. The fact that some mean DDD and duration values are higher in both men and women than for all patients is explained by these missing data.

substance group at least once per quarter during a patient year. While in 2006 the figure was close to 25% in all three substance groups, the groups differed in how they developed over the following years. While for BZD and ZD there were steady decreases to 18.9% and 19.6%, respectively, the prevalence among OA patients increased by about 4% during the same period.

In all substance groups, the prevalence rates of long-term prescriptions were higher for women than

for men (*eTable 2*). However, far larger differences were noted among the various age groups. In 2006, 14% of the 30- to 44-year-old BZD patients were prescribed the medication for a whole year, against one third of the 75+ age group. While in the group of the 30- to 44-year-old BZD patients this proportion fell by only 2% over the following years, a decrease of almost 10% was noted for the oldest BZD patients. The differences were far less pronounced for patients taking ZD.

FIGURE 3

Long-term use (prevalence)

Prevalence of long-term prescriptions of medications with dependence potential among all patients with prescriptions of these substances during the years from 2006 to 2015

An increase in the prevalence of long-term prescriptions with advancing age was also noted among OA patients. However, the proportions increased almost continuously in all age groups between 2006 and 2015 (*eTable 2*).

Discussion

The findings presented above demonstrate that BZD and ZD have lost some of their importance as prescription drugs in recent years. However, patients in the 60+ age group still commonly use BZD and take them over prolonged periods of time—usually many years. Nevertheless, among these patients the amount of drug administered is usually low and in most cases the dose is not increased. The negative consequences of such low-dose dependence can still be severe, with particular reference to fractures related to falls following intake of the medication (6, 20, 21).

Furthermore, in clinical practice ZD are now often prescribed instead of BZD (22). It is now generally accepted that especially the prolonged use of zolpidem can result in misuse and dependence (23–25). Furthermore, use of ZD—like BZD—significantly increases the risk of falls, and thus of fractures (26). In our study, both the prevalence rates for the (long-term) prescription of ZD and the size of the prescribed dose

showed a slightly decreasing trend. There seems to be growing awareness among medical practitioners that ZD are not a risk-free alternative to BZD.

In 2016, about one-fifth of the patients treated with either BZD or ZD received their respective medications over a whole year (or longer). The reasons for such long-term use cited by Olfson et al. (27) include, among others, treatment of persistent anxiety disorders with BZD, the lack of promising alternative treatment options (especially for sleep disturbances), the lack of motivation of older patients to reduce or discontinue their use of this medication, and the time constraints on physicians. Furthermore, Martinsson et al. (28) showed in their analysis of Swedish prescription data for the years 2006 to 2008 that geriatricians and psychiatrists prescribed psychotropic drugs less frequently than primary care physicians. Possibly the latter lacked both specific knowledge of the risks associated with the use of BZD and ZD in older patients and awareness of alternative treatment strategies.

With regard to OA, our study results indicate that epidemic use, as seen in North America (29), is currently not found in Germany.

Nevertheless, the increase in long-term OA prescription arouses concern. While cancer patients may generally require OA treatment over prolonged

periods of time, there are few other conditions where treatment for longer than 6 months is indicated (14).

In conclusion, it can be stated that the treatment of pain patients with opioids is certainly effective, but always associated with risks, which need to be assessed and evaluated on an individual basis. The current German clinical practice guidelines on long-term opioid treatment for chronic non-cancer pain provide valuable guidance (14). However, additional measures should be implemented to limit the number of opioid prescriptions to the level which is medically required. In this respect, White (30) and Compton et al. (31) mention, apart from continuing medical education for prescribing physicians, take-back programs for drugs that are no longer needed, increased use of OA containing naloxone as an additional active ingredient, and especially the establishment of drug monitoring programs. Using the methodology we chose for this study, such a monitoring program could be implemented in the short term and at reasonable financial outlay for OA, hypnotics and sedatives, and any other substance group of interest (32).

Limitations

The prescriptions of BZD and ZD billed with the German national health insurances (GKV) only account for a portion of all prescribed medications. For 2012, for example, it is assumed that the BZD billed to the GKV accounted for about 45% of all dispensed BZD packages (ZD: 50%) (33). Furthermore, it cannot be ruled out that some patients had some of their prescriptions filled in pharmacies billing via the NARZ and some in pharmacies using other settlement agents. In these patients, both the prescribed dose and the prescription duration would be underestimated.

Another limitation is the assumption that all tablets in the prescribed packages are taken. In clinical practice, however, physicians often recommend lower doses or the patients either stop taking the medication early or continue taking it but at a lower dose (34). In such cases, the amount actually taken would be overestimated.

Patients whose sex was not known (between 5% and 12%, depending on the year) were found to have a significantly shorter duration and lower dose for all three substance groups analyzed. Thus, in the sex-related analyses, these parameters are slightly overestimated with regard to their absolute values.

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Conflict of interest statement

PD Uwe Verthein has received reimbursement of travel expenses from Sanofi Aventis and Molteni Farmaceutici as well as reimbursement of travel expenses and lecture fees from Mundipharma.

The remaining authors declare that no conflict of interest exists.

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Key Messages

- In patients with benzodiazepine prescriptions, the proportion being prescribed a medication with the active ingredient lorazepam increased from 17.1% in 2006 to 41.0% in 2016, whereas the percentage of diazepam prescriptions was largely constant (about 22% and 24%, respectively).
- In patients receiving Z-drugs, the proportion with prescriptions for zopiclone increased from 58.7% to 68.6%, while the share of zolpidem prescriptions decreased from 43.5% to 33.4% during the same period.
- Especially elderly patients >65 years of age were frequently prescribed benzodiazepines. At the same time, this age group saw the largest decrease in benzodiazepine prescriptions.
- Contrary to the recommendations of the relevant guidelines, many patients treated with benzodiazepines or Z-drugs were prescribed these medications over a whole year. Opioid analgesic prescriptions showed a slight upward trend.
- With regard to the use of medications with dependence potential, there is a need for thorough training of prescribing physicians and improved patient education, especially for the elderly.

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► Supplementary material

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Problematic Medication with Benzodiazepines, Z-drugs, and Opioid Analgesics

An Analysis of National Health Insurance Prescription Data From 2006–2016

by Sven Buth, Rüdiger Holzbach, Marcus-Sebastian Martens, Eike Neumann-Runde, Ommo Meiners, and Uwe Verthein

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eMETHODS

This section describes in more detail the underlying data and some of the terminology used.

Description of the database

In the German federal states Hamburg, Bremen, Schleswig-Holstein, and Lower Saxony, just over 11 million people are covered by health insurance from statutory providers (GKV) (members and their relatives, voluntary members, and pensioners) (17). Medical prescriptions filled for these patients are usually forwarded to pharmacy data centers where prescription data are processed and billed to the health insurances. The largest such in Northern Germany is NARZ/AVN, which, depending on federal state and calendar year, has between 65% and 91% of all pharmacies under contract.

The dataset processed by NARZ contains all prescriptions issued by statutory health insurer-accredited physicians to patients resident in the above four federal states who, during the years from 2006 to 2016, were issued at least one GKV prescription for a medication with an active ingredient from the substance groups benzodiazepines, Z-drugs, opioid analgesics, antidepressants, amphetamines, barbiturates, and opioid substitute medications and who had the prescription filled in a pharmacy contracted to NARZ for billing purposes. For the analyses presented in this article, only prescription data for the first three substance groups listed above were used. Medicines containing active ingredients of the ATC code groups N05AB and N05CD as well as N03AE01 were classed as benzodiazepines. Tetrazepam (M03BX07), which was frequently prescribed in earlier years, was suspended across the EU in August 2013; we therefore excluded it from all analyses, including those of prescriptions written prior to August 2013. If tetrazepam had been included, the prevalence rate for benzodiazepines would have been about 5% for the period 2006 to 2012.

Medicines containing active ingredients of the ATC code groups N05CF01, N05CF02, and N05CF03 were classed as Z-drugs. Opioids are contained in numerous classes of medicines (analgesics, anesthetics, opioid substitutes, and antitussives). In our study, only medications classed as analgesics (ATC group N02A) were included in the analyses. It should be noted, however, that codeine medications were excluded from the analyses—as in the study by Schubert et al. (13). Furthermore, dihydrocodeine medications (N02AA08) were included in the analysis only if pain relief was their primary indication.

Besides the date when the medication was dispensed to the patient and drug-related information (German Pharmaceutical Central Number [PZN], ATC code, ingredients, dose), the patient's year of birth and sex (if known) were integrated. Unfortunately, the latter is not directly

documented on prescriptions. In order to enable sex-specific analyses, the NARZ/AVN allocated a sex to a patient based on their given name. However, this was not possible in all cases, because, for example, some names are used for both sexes. Consequently, a significant number of patients—between 5% and 12%, depending on the year—could not be included in the sex-specific analyses.

Definition of patient years, long-term prescriptions and duration of use

In our article, we differentiate between calendar year and patient year. Patient year refers to the period of 12 months starting with the first prescription in a calendar year; thus, it represents a patient observation year. For example: A patient has her first benzodiazepine prescription in the 2006 calendar year filled on 1 July. The patient year for this person is the observation period from 1 July 2006 to 30 June 2007. Thus, the further duration- or dose-related analyses include all benzodiazepine prescriptions within this period.

As the result of this definition of a patient year, although prevalence rates can be reported for 2016, duration- and dose-related analyses cannot be performed as they would require prescription data from 2017, which were not available for our study.

Persons with long-term prescriptions are patients who in every quarter of a patient year received at least one prescription of the substance concerned.

The duration of medication use is calculated based on the interval between the first and last filled prescription of a substance group within a patient year together with the assumed duration of intake of the last medication prescribed. The average daily dose is calculated from the ratio between the prescribed dose per patient year (based on defined daily doses [DDD]) and duration.

eTABLE 1

Prevalence of prescriptions of medications with dependence potential during the years from 2006 to 2016 by sex and age group

		Sex		Age (years)				
		Male	Female	≤ 29	30–44	45–59	60–74	≥ 75
Benzodiazepines	2006	2.2%	4.6%	0.6%	2.0%	3.5%	6.3%	11.8%
	2007	2.2%	4.2%	0.6%	1.9%	3.2%	5.7%	10.9%
	2008	2.2%	4.1%	0.6%	1.9%	3.2%	5.6%	10.7%
	2009	2.1%	3.8%	0.6%	1.8%	2.9%	5.2%	9.7%
	2010	1.9%	3.5%	0.6%	1.7%	2.7%	4.7%	8.5%
	2011	1.8%	3.3%	0.6%	1.6%	2.6%	4.4%	7.9%
	2012	1.8%	3.1%	0.5%	1.5%	2.4%	4.2%	7.4%
	2013	1.7%	3.0%	0.6%	1.5%	2.3%	3.9%	6.8%
	2014	1.7%	2.8%	0.6%	1.5%	2.3%	3.7%	6.3%
	2015	1.6%	2.7%	0.6%	1.4%	2.2%	3.4%	6.0%
	2016	1.5%	2.5%	0.5%	1.3%	2.0%	3.2%	5.6%
Z-drugs	2006	0.7%	1.4%	0.1%	0.6%	1.2%	2.0%	3.2%
	2007	0.7%	1.3%	0.1%	0.6%	1.2%	1.9%	3.1%
	2008	0.8%	1.4%	0.1%	0.7%	1.2%	2.0%	3.2%
	2009	0.8%	1.4%	0.1%	0.7%	1.2%	2.0%	3.2%
	2010	0.7%	1.3%	0.1%	0.6%	1.1%	1.9%	2.9%
	2011	0.7%	1.3%	0.1%	0.7%	1.2%	1.9%	2.8%
	2012	0.7%	1.2%	0.1%	0.6%	1.1%	1.8%	2.7%
	2013	0.7%	1.2%	0.1%	0.6%	1.1%	1.7%	2.5%
	2014	0.7%	1.2%	0.1%	0.6%	1.0%	1.6%	2.4%
	2015	0.6%	1.1%	0.1%	0.6%	1.0%	1.5%	2.3%
	2016	0.6%	1.0%	0.1%	0.5%	0.9%	1.4%	2.2%
Opioid analgesics	2006	3.1%	5.1%	0.4%	2.0%	4.3%	7.7%	15.4%
	2007	3.3%	5.1%	0.4%	2.1%	4.4%	7.7%	15.5%
	2008	3.4%	5.2%	0.4%	2.2%	4.5%	7.8%	15.7%
	2009	3.4%	5.2%	0.4%	2.2%	4.4%	7.8%	15.5%
	2010	3.5%	5.3%	0.4%	2.3%	4.5%	7.9%	15.5%
	2011	3.5%	5.4%	0.4%	2.3%	4.5%	7.9%	15.7%
	2012	3.7%	5.6%	0.4%	2.4%	4.6%	8.1%	16.3%
	2013	3.7%	5.6%	0.5%	2.4%	4.5%	7.9%	15.8%
	2014	3.7%	5.7%	0.5%	2.4%	4.6%	8.0%	15.9%
	2015	3.8%	5.8%	0.5%	2.4%	4.7%	7.9%	16.1%
	2016	3.8%	5.8%	0.5%	2.4%	4.8%	7.9%	16.1%

Between 5% and 12% of patients, depending on the year, could not be included in the sex-specific analyses, because their sex was not known.

eTABLE 2

Prevalence of long-term prescriptions of medications with dependence potential in all patients with prescriptions of these substances during the years from 2006 to 2015 by sex and age group

		Sex		Age (years)				
		Male	Female	≤ 29	30–44	45–59	60–74	≥75
Benzodiazepines	2006	24.1%	25.1%	6.9%	14.0%	20.3%	26.8%	33.3%
	2007	23.4%	25.0%	6.6%	13.7%	19.9%	26.6%	33.1%
	2008	23.1%	24.5%	6.3%	13.4%	19.7%	26.2%	32.5%
	2009	21.2%	22.2%	6.0%	13.0%	18.6%	24.0%	28.9%
	2010	21.5%	22.3%	6.3%	12.9%	18.6%	24.2%	29.3%
	2011	20.7%	21.2%	5.8%	12.7%	18.1%	23.1%	27.8%
	2012	19.6%	19.9%	6.0%	12.6%	17.2%	22.0%	25.3%
	2013	19.3%	19.9%	5.9%	12.1%	17.0%	22.4%	25.5%
	2014	18.8%	19.2%	6.2%	11.5%	16.6%	22.0%	24.6%
	2015	18.6%	19.1%	6.6%	12.1%	17.0%	21.6%	23.7%
Z-drugs	2006	22.9%	25.6%	6.1%	12.3%	20.3%	28.4%	32.7%
	2007	22.6%	26.4%	6.2%	12.6%	19.8%	29.0%	33.6%
	2008	22.0%	25.8%	5.5%	11.5%	19.0%	28.7%	33.5%
	2009	19.5%	22.4%	4.8%	10.8%	16.7%	24.8%	28.7%
	2010	20.1%	23.0%	5.0%	10.6%	16.8%	26.0%	30.1%
	2011	18.9%	21.9%	4.9%	10.0%	15.8%	24.8%	28.6%
	2012	18.0%	20.6%	4.1%	10.1%	15.0%	23.4%	26.4%
	2013	18.5%	21.2%	4.4%	10.7%	15.2%	23.7%	27.5%
	2014	18.0%	21.0%	4.4%	10.9%	15.2%	23.0%	27.1%
	2015	18.0%	20.5%	4.6%	11.2%	15.1%	22.8%	25.9%
Opioid analgesics	2006	22.8%	25.7%	5.8%	14.8%	22.4%	26.2%	29.7%
	2007	22.7%	27.2%	6.0%	14.6%	22.8%	27.1%	31.1%
	2008	23.6%	28.6%	6.1%	15.0%	23.8%	28.3%	33.0%
	2009	24.3%	29.8%	5.9%	15.3%	24.4%	29.3%	34.4%
	2010	24.5%	29.9%	6.3%	15.4%	24.1%	29.3%	34.8%
	2011	24.9%	30.5%	6.3%	15.8%	24.3%	29.7%	35.4%
	2012	24.3%	29.5%	6.0%	15.4%	23.4%	29.2%	34.0%
	2013	25.3%	31.1%	6.4%	15.5%	24.5%	30.7%	35.8%
	2014	25.2%	30.9%	6.5%	14.9%	24.2%	30.5%	35.9%
	2015	25.4%	31.2%	6.6%	15.0%	24.4%	30.6%	36.0%

Between 5% and 12% of patients, depending on the year, could not be included in the sex-specific analyses, because their sex was not known.