ORIGINAL REPORT

Exposure to benzodiazepines (anxiolytics, hypnotics and related drugs) in seven European electronic healthcare databases: a cross-national descriptive study from the PROTECT-EU Project

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ABSTRACT

Purpose Studies on drug utilization usually do not allow direct cross-national comparisons because of differences in the respective applied methods. This study aimed to compare time trends in BZDs prescribing by applying a common protocol and analyses plan in seven European electronic healthcare databases.
Methods Crude and standardized prevalence rates of drug prescribing from 2001–2009 were calculated in databases from Spain, United Kingdon (UK), The Netherlands, Germany and Denmark. Prevalence was stratified by age, sex, BZD type [(using ATC codes), i.e. BZD-anxiolytics BZD-hypnotics, BZD-related drugs and clomethiazole], indication and number of prescription.
Results Crude prevalence rates of BZDs prescribing ranged from 570 to 1700 per 10 000 person-years over the study period. Standardization by age and sex did not substantially change the differences. Standardized prevalence rates increased in the Spanish (+13%) and UK databases (+2% and +8%) over the study period, while they decreased in the Dutch databases (−4% and −22%), the German (−12%) and Danish (−26%) database. Prevalence of anxiolytics outweighed that of hypnotics in the Spanish, Dutch and Bavarian databases, but the reverse was shown in the UK and Danish databases. Prevalence rates consistently increased with age and were two-fold higher in women than in men in all databases. A median of 18% of users received 10 or more prescriptions in 2008.
Conclusion Although similar methods were applied, the prevalence of BZD prescribing varied considerably across different populations. Clinical factors related to BZDs and characteristics of the databases may explain these differences. Copyright © 2015 John Wiley & Sons, Ltd.

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INTRODUCTION

BZDs are one of the most widely used drug classes. Their pharmacological properties confer a broad range therapeutic applicability in anxiety, insomnia, panic attacks, epilepsy, muscle spasms and pre-surgical stress.[1] Their use has been a matter of concern among public health regulators in different countries because of the associated risks with long-term exposure.[2–4]

Although many drug utilization studies have been published over the last 20 years, which focused on prescribing and use of BZDs in different countries or regions, comparisons are difficult because of differences in methodology. Moreover, only a few studies were designed for direct cross-national comparison.[5–9]

Within this context, this study aimed to describe the patterns of BZD prescriptions in different European databases using a common methodology and definitions. We also included in the study the use of hypnotics separately as BZD-related hypnotics (Z-drugs) that have been proposed to replace BZDs for their allegedly better safety profile.[10]

The present study is part of PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium) (http://www.imi-protect.eu/), a European consortium in the field of pharmacoepidemiology and pharmacovigilance, with the general aim of developing a standardized way to conduct pharmacoepidemiological studies that enable comparisons across countries and databases.

PATIENTS AND METHODS

Setting and data collection

Seven databases representing five European countries, participated in this descriptive study: The Spanish "Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria" (BIFAP),[11] the Clinical Practice Research Datalink (CPRD), formerly known as General Practice Research database (GPRD),[12] and the Health Improvement Network (THIN) from the United Kingdom (UK),[13] two databases participating in the Dutch Mondriaan project: the Netherlands Primary Care Research database (Mondriaan-NPCRD) which is maintained by NIVEL, and the Almere Health Care Group (Mondriaan-AHC) database,[14] the Bavarian Association of Statutory Health Insurance Physicians claims database (Bavarian)[15] and, finally, the Danish national registries

(DKMA).[16] All databases participating have been described in detail elsewhere.[17] The study was based on a common protocol and data specifications applied to all analyses in the individual databases.

Source population

The study population consisted of all patients in the corresponding databases during the period from 1 January 2001 until 31 December 2009. For Mondriaan-AHC data for the year 2009 were not available, and for the Bavarian database, the study period was shorter (2004–2008). For each database, all patients with valid data within the study period were included. Each patient was followed up from the start of the study period or enrolment of the patient or practice into the database or the date the practice became up to research standard (whichever occurred last) until the patient left the practice/database or the practice did not contribute further information to the database or the end of the study period (whichever occurred first).

Drugs

The Anatomical Therapeutic Chemical (ATC) Classification System[18] was used for the classification of drugs of interest, i.e.: N05BA (anxiolytics—benzodiazepine derivatives), and hypnotics under N05CD (hypnotics and sedatives—benzodiazepine derivatives) and N05CF (hypnotics and sedatives—benzodiazepine-related drugs or Z-drugs). Although clomethiazole (N05CM02) was not prescribed in the Bavarian and Dutch databases during the study period, this drug was also included because its use as a hypnotic is non negligible in Spain. BZDs primarily used for other indications (e.g. tetrazepam as muscle relaxant and clonazepam for epilepsy) were not included in our study.

Although the available drugs differ among countries, the main drugs are essentially the same (see the complete list in Table S1 available online).

In the BIFAP, THIN, CPRD, Mondriaan-NPCRD and Bavarian databases the prescription of the drug of interest was the indicator of exposure, while in DKMA the indicator was the dispensing of the drug. In the Mondriaan-AHC database, both prescription and dispensing data were available and used to indicate exposure.

Analysis

In each database, the annual period prevalence of BZD prescribing was estimated by dividing the number of

patients who received one or more prescription (or dispensing in the case of DKMA or prescription/dispensing in the case of the Mondrian-AHC database) by the total number of person-years of follow-up in every calendar year of the study period (2001–2009). Because of the dynamic nature of the databases, where patients can come in and out and have variable durations of follow-up time, person-years were considered as the most appropriate denominator. In the Bavarian database, only the quarter of the year in which the prescription was written was available, so for this database we used the number of patients at mid-year as the denominator. In calculating annual prevalence for 2008, the number of patients at 1 June included in different databases was also provided.

In order to adjust for differences in age and sex distribution between databases, we standardized the prevalence rates using the Eurostat 2008 population.[19] Prevalence rate ratios (PRR) were calculated for both crude and standardized rates in order to compare prevalence rates between databases; the median of all prevalence rates in the different databases was used as reference.

Specific crude prevalence rates were also provided by separate therapeutic groups (anxiolytics (N05BA) and hypnotics (N05CD, N05CF and N05CM02)), age groups (in 10-year categories) and sex.

The total number of prescriptions was obtained for the year 2008. Mean prescription per patient was calculated by type of BZD. We also calculated the percentage of prescribing in four categories of number of prescriptions (1, 2–4, 5–9 and 10+) among those with at least a prescription.

Finally, the recorded indication for prescribing was explored in all databases for 2008. Patients receiving one of the drugs of interest were classified in one of the following mutually exclusive categories: anxiety disorders (alone or with other indication—excluding depression), sleep disorders (alone or with any indication—excluding anxiety and/or depression), depressive disorders (with either or both anxiety and sleep

disorders), depressive disorders (alone or with any indication under "other"), other (miscellaneous category including muscular relaxation, alcohol withdrawal or epilepsy) and unknown (codes other than those mentioned above). DKMA reported only one category for depression regardless whether patients additionally had anxiety or sleep disorders. Potential indication was first identified by checking for indication on the prescription date, followed by looking for the indication within a defined time window of three months before and after the date of the prescription. When the data was not available on the prescription date a search in the time window was performed. A sensitivity analysis was also performed extending the time window to any time during the study period prior to the prescription date (Supplementary Table S2 online).

The study was registered in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) registry of studies.[20]

RESULTS

Prevalence rates

In 2008 (the last calendar year available in all databases), the seven databases participating in the study provided information from 1.7 million patients being prescribed BZD, from a total population of more than 24 million persons-years (Table 1).

The overall prevalence rate of BZDs prescriptions varied considerably across databases, with the highest rate in BIFAP database (around 1600 per 10 000 person-years) and the lowest in the Bavarian and UK databases (around 570 per 10 000 person-years). The standardization by sex and age did not substantially change the observed differences (Table 1).

Trends in prevalence rates, crude as well as age- and sex-standardized, are presented in Figure 1. Comparison of crude rates for the latest available calendar year with

Table 1. Crude and standardized prevalence rates and prevalence rate ratios of BZDs use in 2008 in the seven participating databases

DBs	BZD prescribing	Persons at 1st June in databases	Person-years in databases	Prevalence rate (per 10 000 p-y)	PRR*	Age and sex standardized prevalence rate (per 10 000 p-y)	Age and sex-standardized PRR*
BIFAP	231 729	1 441 011	1 424 572	1626.7	2.1	1598.1	1.9
CPRD	258 353	4 771 361	4 348 431	594.1	0.8	590.8	0.7
THIN	213 820	3 704 927	3 713 072	575.9	0.7	586.6	0.7
Mondriaan-AHC	13 941	140 818	142 819	976.1	1.2	1186.8	1.4
Mondriaan-NPCRD	25 912	346 332	330 477	784.1	1.0	835.9	1.0
Bavarian[†]	485 058	8 558 315	8 558 315	566.8	0.7	477.2	0.6
DKMA	437 881	5 242 538	5 222 891	838.4	1.1	853.3	1.0

BZD: benzodiazepine anxiolytics and hypnotics and related drugs; PRR: prevalence rate ratio.
*Reference category to calculate PRR was the median value of all prevalence rates in the databases for 2008.
[†]Person-years not available, denominator were patients at 1 July; person-years were calculated assuming a complete follow-up.
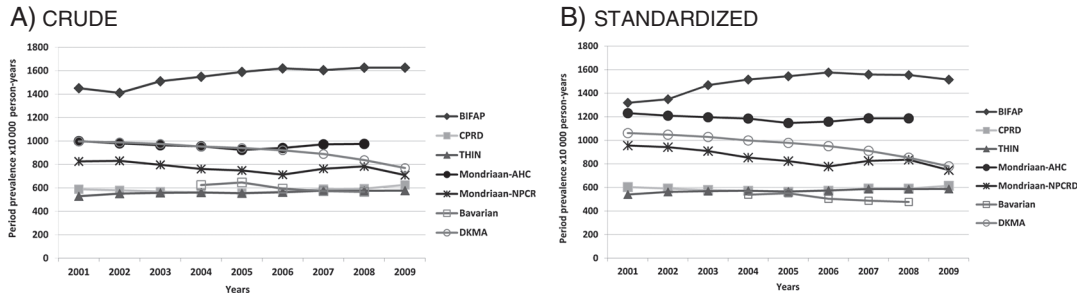
A) CRUDE

B) STANDARDIZED

Figure 1. Period prevalence rates of BZDs use by year in the participating databases. A) crude rates and B) standardized rates by age and sex. [Change made after first online publication: y-axis scale in (A) corrected from 'x10 0000' to 'x10 000']

the first year showed an increase in BIFAP (+11%), CPRD (+6%) and THIN (+8%); and a decrease in AHC (−2%), NPCRD (−14%), Bavarian (−9%) and DKMA (−23%) databases. When rates were standardized by age and sex, trends showed an increase in BIFAP (+13%), CPRD (+2%) and THIN (+8%) while a decreasing trend was observed in AHC (−4%), NPCRD (−22%), Bavarian (−12%) and DKMA (−26%).

Throughout the study period, the prevalence of prescriptions of BZDs classified as anxiolytics was 4-times higher than that of hypnotics (including BZDs, Z-drugs and clomethiazole when available) in BIFAP (i.e. 1439.3 vs. 363.2 per 10 000 person-years for 2008), 1.3-times higher in the Bavarian database (i.e. 347.8 vs. 266.4 per 10 000 person-years for 2008) and 1.5-times higher in the Mondriaan-AHC database (i.e. 666.7 vs. 457.0 per 10 000 person-years for 2008), whereas in the UK databases, CPRD and THIN, and in DKM, the prevalence for hypnotics prescriptions outweighed that of anxiolytics, by a factor of approximately 1.2 (i.e. 355.6 vs. 302.8, 359.6 vs. 291.5 and 523.5 vs. 436.7, per 10 000 person-years respectively for 2008). Almost no differences were observed in the Mondriaan-NPCRD databases. Trends over time were essentially similar for both anxiolytics and hypnotics (Figure 2).

Among hypnotics, the prevalence of Z-drugs was higher than BZD-hypnotics in the Bavarian database (2–3 times higher) and DKMA (2–5 times higher)

databases for the whole period. For the UK databases, prevalence of Z-drugs prescriptions was lower than BZDs at the start of the study period, but from 2004 onwards, it was steadily higher. In the Spanish and Dutch databases prevalence for BZD-hypnotics was higher than for Z-drugs over the study period (1.5 and 4–6 times, respectively) (see Figure 3). Clomethiazole use was negligible in the UK and DKMA databases; in the BIFAP database, it represented about 6% of the total use of hypnotics (Figure 3).

Prevalence rates by age and sex

The prevalence of BZDs prescriptions increased steadily with age in all databases both in females and males, although the slopes were higher in females (Figure 4). This was observed in all age categories from 20 years and older. For all databases, the age-specific prevalence rates were about 1.5 to 2 times higher for women than men, and this difference was particularly obvious in patients over 50 years of age.

Trends in age-specific prevalence rates showed an important decrease in use in older ages (60 years and older) over the study period in most countries (with the exception of BIFAP), while prevalence remained stable (or showed a slight increase in some databases) among the younger ones (Supplementary Figure S1 online), with hardly no differences by sex.
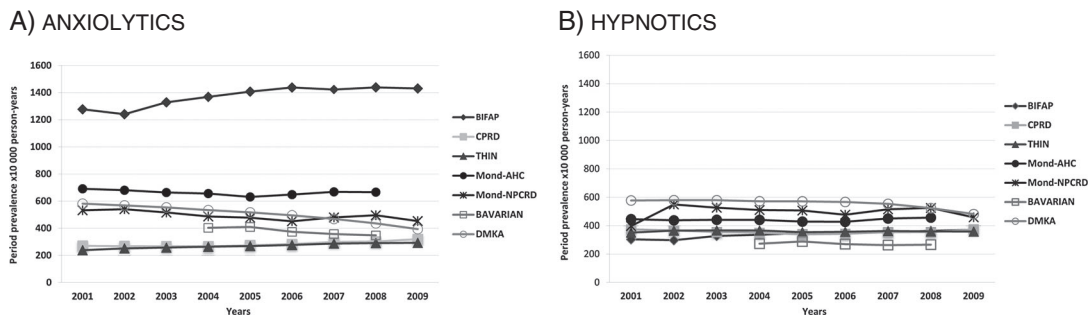
A) ANXIOLYTICS

B) HYPNOTICS

Figure 2. Period prevalence rates of BZDs use according to the ATC classification: A) anxiolytics (N05BA) and B) hypnotics (N05CD, N05CF and N05CM02). Crude rates
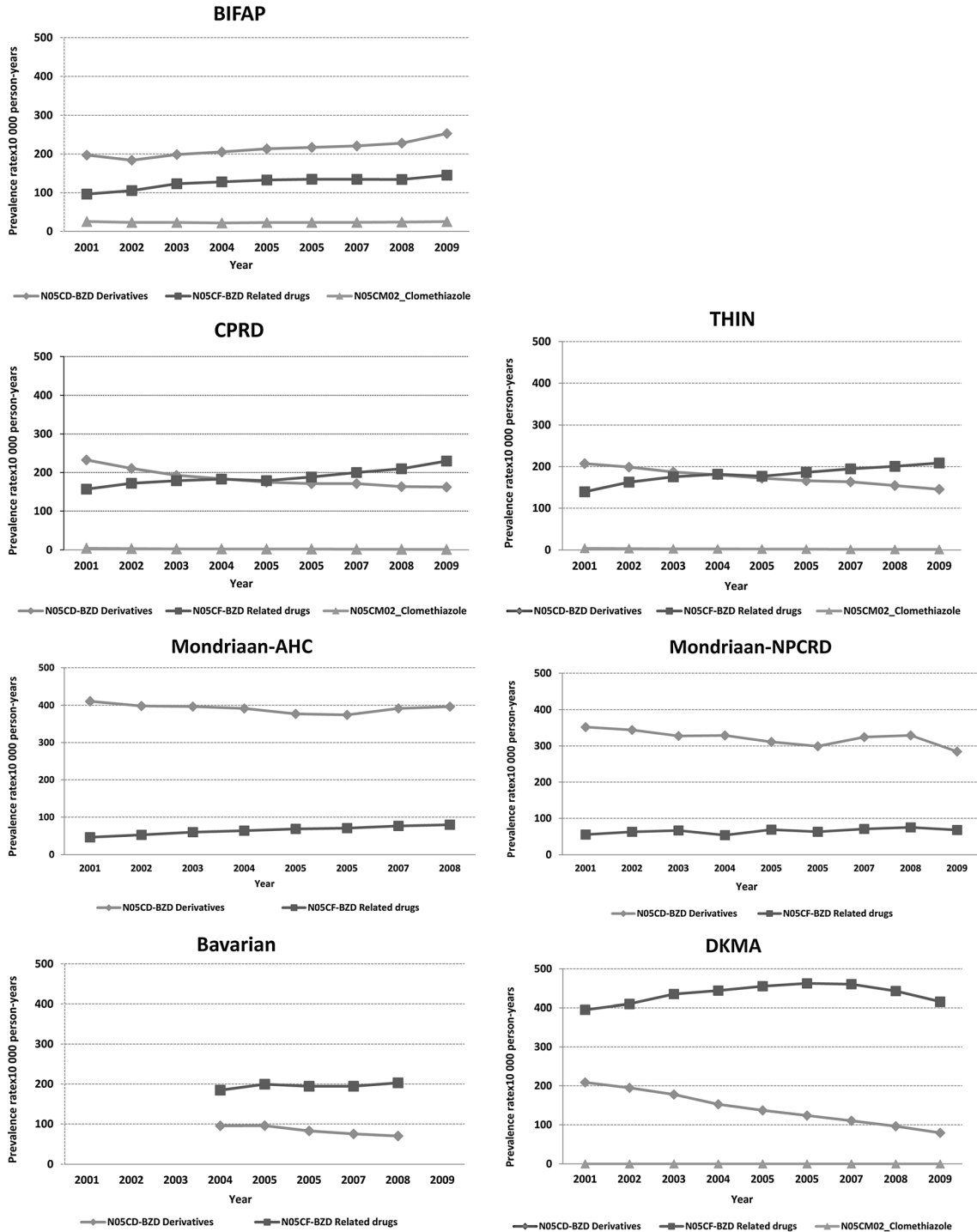
Figure 3. Trends in prevalence of the use of hypnotics (N05CD, N05CF and N05CM02). Crude rates

Number of prescriptions

The mean number of prescriptions per patient in 2008 was rather similar in the different databases both for anxiolytics (ranged from 4 to 5) and for hypnotics (ranged from 4 to 6). Only the Bavarian databases presented distinct low numbers for anxiolytics and hypnotics (2 and 3, respectively). Most patients received 4 or less prescriptions per year in all databases (in 2008; median 66.3%, range 53.7–83.8%). Of note, a considerable proportion of users received 10 or more prescriptions per year (in 2008; median 18.1%, range: 1.9–27.9%) (Table 2).
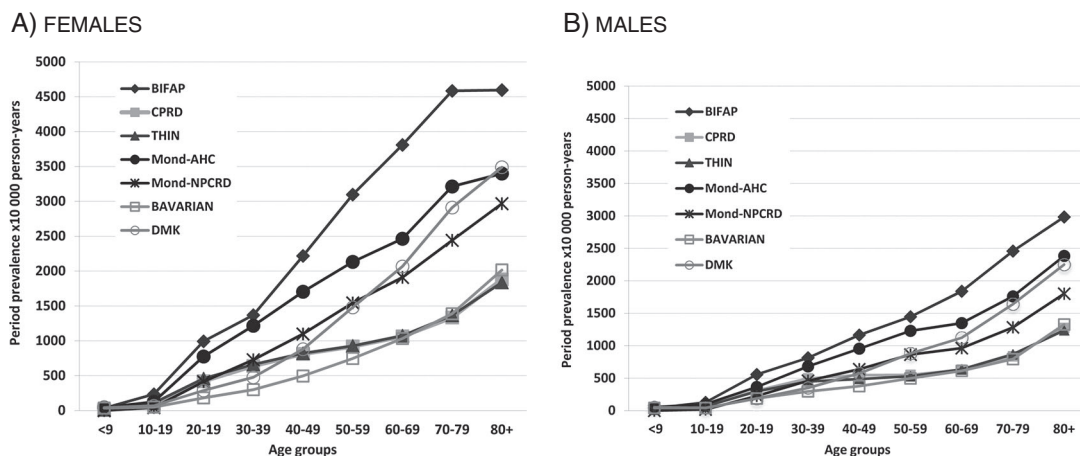
Figure 4.   Prevalence use rates of BZDs by sex and age for 2008 in different databases. Crude rates

Potential indication

In searching for registered indication three months around the first prescription, the linkage of prescriptions with their indication using diagnostic codes proved to be quite difficult in most databases with a percentage of unknown ranging from 21.7% to 82.2%. Among known indications, sleep disorders (without anxiety) were the most often recorded diagnosis temporally related with the prescription, (median 13.3%; range: 7.0%–76.0%). The recording of anxiety and related disorders also varied among databases (median = 12.7%; range: 1.6%–27.7%) (Figure 5). A sensitivity analysis searching diagnostic codes for indication any time during the study period prior to the prescription date, resulted in a marked decrease of the unknown category (Supplementary Figure S2 online).

DISCUSSION

This collaborative European study provides a unique and updated overview of the prevalence of BZDs prescribing as well as trends over a 9-year period, in large populations derived from seven electronic health databases from five Western European countries. As uniform methods and analysis were applied, variations in results may be explained according to the differences in database characteristics and in clinical aspects related to the use of BZDs.

We found remarkable differences in prevalence rates of BZD use, which are not attributable to differences in age or sex distribution in their respective populations. Although differences across countries in the prevalence of disorders for which these drugs are indicated cannot be ruled out, it seems that most differences can be attributed to diverse prescription habits of physicians, as it has been shown in previous studies even within the same country.[21–23] Added to this, the attitudes of patients towards mental health help-seeking can vary across countries, and this may also help to explain the differences in prescribing.[24,9]

To the best of our knowledge, previous collaborative European studies on BZD use are scarce. Only five studies published in the last 15 years were identified, with a cross-national comparison.[5–9] Other published studies are country or region specific.[25–32] Most of these studies investigated the broader group of psychotropic medication, including other drugs different from BZDs, which yielded different exposure definitions.[5,6,8,28–30] In most, information was obtained from questionnaires.[5,6,9,26,28,29] Age ranges and study period also varied largely among studies. In sum, all these factors make the comparison with other studies difficult—as already noted in a previous publication.[33] Nonetheless, all studies performed in adults captured two constant elements in BZD use: the higher prevalence in women and the steadily increasing use with age.[5,6,9,27,29,31,32]

Our study shows that standardized prevalence rates remained rather stable over the study period in three databases (CPRD, THIN and Mondriaan-AHC), decreased in three (Mondriaan-NPCRD, Bavarian and DKMA) and increased in one (BIFAP). A closer look at the trends by age groups showed that a decreasing trend was the pattern for most databases among the elderly. This is probably the consequence of the initiatives taken by official bodies[2] and the scientific community,[34–39] in order to rationalize the use of BZDs. The Spanish BIFAP is the only database where a steady and relevant increase was observed over the study period, which is consistent with results from other studies.[3,25] Population databases may be an important tool to assess trends

Table 2. Number (percentages) of patients by number of prescriptions in the different databases in 2008

	Total patients prescribed BZDs	Patients prescribed by BZD type		Total number of prescriptions by BZD type		Mean of prescriptions per patient by BZD type		Number (percentage†) of patients by number of prescriptions			
		Anx*	Hyp*	Anx	Hyp	Anx	Hyp	1 prescription	2–4 prescription	5–9 prescription	10+ prescriptions
BIFAP	231 729	205 032	51 746	931 588	265 622	4.5	5.1	68 861 (29.7)	55 659 (24.0)	42 466 (18.3)	64 743 (27.9)
CPRD	258 353	131 658	154 634	613 039	942 286	4.7	6.1	108 790 (42.1)	59 684 (23.1)	34 938 (13.5)	54 941 (21.3)
THIN	213 820	108 237	133 512	496 829	824 111	4.6	6.2	90 281 (42.2)	49 551 (23.2)	30 273 (14.2)	43 715 (20.4)
Mondriaan-AHC	13 941	9522	6527	41 858	35 915	4.4	5.5	5576 (40.0)	3875 (27.8)	1962 (14.1)	2528 (18.1)
Mondriaan-NPCRD	25 912	16 401	12 952	66 875	57 415	4.1	4.4	9485 (36.6)	9045 (34.9)	4124 (15.9)	3258 (12.6)
Bavarian	485 058	297 670	227 977	662 721	631 397	2.2	2.8	225 048 (46.4)	181 573 (37.4)	69 141 (14.3)	9296 (1.9)
DKMA	437 881	228 081	273 449	113 177	120 041	5.0	4.4	146 956 (33.6)	143 089 (32.7)	81 056 (18.5)	66 780 (15.2)

Anx: anxiolytics; Hyp: hypnotics.
*Number of patients prescribed anxiolytic and hypnotic does not add up to total patients prescribed BZDs as some patients can contribute both to anxiolytics and hypnotics prescribing categories.
†Percentage of total patients prescribed BZDs.

and evaluate the effectiveness of prescribing recommendations.

Regarding the prevalence of use of anxiolytics and hypnotics, two different patterns were observed. Anxiolytics were more frequently prescribed than hypnotics in three databases (BIFAP, Bavarian and Mondriaan-AHC), which is in line with previous published results,[3,5–9,25] whereas hypnotics were more frequently used in three other databases (CPRD, THIN and DKMA), as also described previously.[2,6,29] These differences may have several explanations. First, the prescription of BZDs and the selection of anxiolytics or hypnotics are influenced by marketing preferences and physician habits rather than by real pharmacological differences. Second, it has been described that patients receiving BZDs for insomnia complaints were treated in a similar percentage with anxiolytics and hypnotics.[40] Third, anxiety and insomnia seem to be intertwined over time,[41] and the choice of the BZD may depend on the most predominant disorder as well as the physicians' experience[42].

This study also shows the remarkable differences in the market uptake of the newer Z-drugs. It seems that these drugs have been more easily introduced in those countries which showed the most remarkable decreasing trends of BZD prescribing (Denmark and Germany). However, it is important to note that these drugs have not been shown to have a lower risk of fractures requiring hospitalization than benzodiazepines,[43] which is one of the major concerns among the elderly, in addition to drug abuse and dependency.

Concerning number of prescriptions, the highest percentage of users might suggest to be considered sporadic users (only one prescription per year) or short-term users (four or less prescriptions per year). However, the percentage of regular or chronic users (10 or more prescriptions per year) continues to be quite high, as shown in previous studies,[26–28,32] and this appears not to be country specific. This matter would deserve a more thorough study in order to analyze the main determinants of chronic use, as a first necessary step to plan interventions to reduce intake.

A remarkably high proportion of prescriptions without any specific recorded indication was observed in the different databases, which was reduced when the search was extended to diagnoses recorded any time during the study period prior to the first prescription. This might be explained by the fact that some diagnoses, such as depressive disorders, are registered only once instead of every time a prescription is filled. Among the known indications, most are related with anxiety and sleep disorders, which is an expected result. Of note, half of the patients who were prescribed
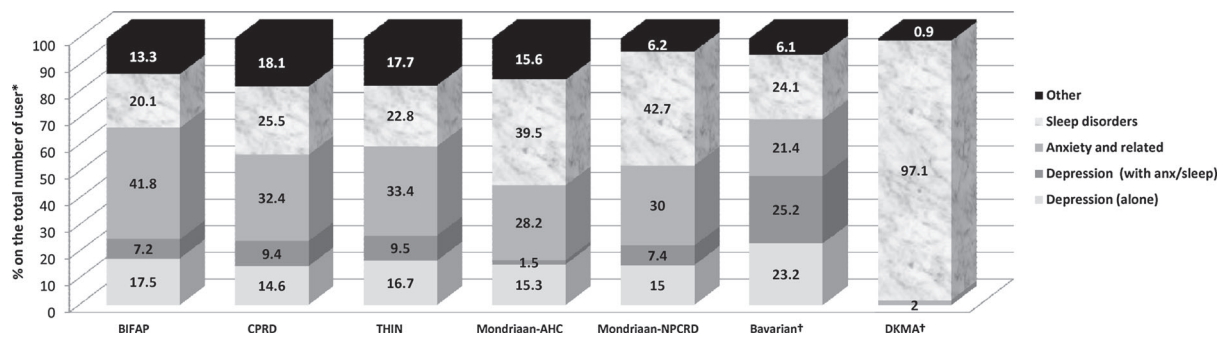
* % Calculated on the total number of users by database excluding category "Unknown" *[Results for "Unknown" were: BIFAP: 78.229 (33.8%); CPRD: 157246 (60.9%); THIN: 135923 (63.6%); Mondriaan-AHC: 11465 (82.2%); Mondriaan-NPCRD: 12172 (47.0%); Bavarian: 172528 (35.6%) and DKMA: 95271 (21.7%)].*

† In the Bavarian and DKMA databases, only the link between prescription and diagnoses was used. DKMA reported only one category for depression regardless patients additionally had anxiety or sleep.

Figure 5. Indications for BZDs in 2008 by searching for registered indications during the 3 months prior to and 3 months post the date of the first BZD prescription in the different databases

BZDs in the Bavarian database had a diagnosis classified under depressive disorders (alone or associated) as the main indication, while in the other databases the proportion was around 25%. Differences in the underlying coding systems may explain these results. In addition, the Bavarian database presented the lowest numbers of both the mean prescriptions per patients and the proportion of chronic user. Explanations could be related to differences in benefit and risk perceptions for BZDs and Z-drugs.[44] Furthermore, a relevant proportion of prescriptions from the private healthcare sector, which are not documented in the Bavarian database, have been described for BZDs and Z-drugs.[45] A wide regional variation of private prescriptions was found for the Z-drugs zolpidem and zopiclone in Germany.[46] Finally, it is possible that this approach was not able to fully address this issue. Our conclusion is that indication appears as a major challenge in pharmacoepidemiological studies; moreover in those databases where information on indication is not directly available, creating the need for studies specifically designed to further investigate the recording of indication and making adapted to the specific characteristics of the database.

Important strengths of this study deserve attention. First, this study estimated prevalence rates of BZD use by counting patients with recorded prescriptions, which eliminate measurement errors because of inadequate recall by respondents. Second, all databases are population-based providing appropriate denominators in persons and person-years. Third, populations included in most GP-based databases are representative of their respective country population (THIN, CPRD, BIFAP and Mondriaan-NPCRD), although it is not possible to assure that prescription habits of GPs participating in these databases are representative of the national

prescribing habits of all GPs. Finally, the Danish Registries include the entire population, and the Bavarian database includes approximately 84% of the population at regional Bavarian level.

Some limitations also need to be addressed. Prescriptions of BZDs outside the primary care setting, such as in-hospital use or private prescribing may not be considered in these databases. Over the counter delivery is not expected to affect results because BZDs are prescription drugs under strict dispensing control in all participating countries. Differences in the coding systems used in the databases may also have produce differences in indication. For those databases registering prescriptions for BZDs, we cannot exclude the possibility that patients did not collect the drug from the pharmacy, this accounted for a 5% in Denmark.[47]

In conclusion, this study shows that analyzing drug utilization in different databases from different countries according to a common protocol is feasible and valuable especially for direct cross-comparisons. In addition, after applying harmonized methods, differences in prescribing prevalence may further be explained by differences in the characteristics of the databases reflecting different aspects related to the use of the BZDs, prescribing habits and/or patient perception. Appropriate comparison of drug utilization across countries gives the opportunity to answer basic questions about prescribing practices and trends which may also help guide public health policies and identify areas in which more research is needed.

SPECIFIC AUTHOR CONTRIBUTION

All authors contributed to the study conception and design. Authors responsible for each database

performed the data extraction and data analysis. CH and FJA wrote the first draft. All authors contributed with critical comments to the final version.

CONFLICT OF INTEREST

C Huerta, V Abbing-Karahagopian, G Requena, B Oliva, Y Alvarez, H Gardarsdottir, M Gil, J Slattery, U Hesse, M Rottenkolber, D Montero, F de Vries and F J de Abajo declare that they have no conflict of interest.

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KEY POINTS
- Drug prescribing prevalence rates of benzodiazepines varied considerably across different European countries included in the study.
- Prevalence trended to increase in the Spanish and United Kingdom databases over the study period, while they decreased in the Danish, Bavarian and Dutch databases. Overall, changes in utilization in either direction were modest.
- All databases consistently showed that the use of benzodiazepines increased with age and was two-fold higher in women than in men.
- Most users of benzodiazepines received four or less prescriptions per year, yet a high proportion received 10 or more prescriptions per year in most countries.
- The analysis of prescribing trends in different databases according to a common protocol is feasible and valuable and may play an important role in pharmacovigilance but also in pharmacoepidemiology and health policy.

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