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Antidepressant prescribing in five European countries: application of common definitions to assess the prevalence, clinical observations, and methodological implications

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ABSTRACT

Purpose: Drug utilization studies have applied different methods to various data types to describe medication use, which hampers comparisons across populations. The aim of this study was to describe the time trends in

antidepressant prescribing in the last decade and the variation in the prevalence, calculated in a uniform manner, in seven European electronic healthcare databases. Methods: Annual prevalence per 10,000 person-years (PYs) was calculated for 2001–2009 in databases from Spain, Germany, Denmark, the United Kingdom (UK), and the Netherlands. Prevalence data were stratified according to age, sex, antidepressant type (selective serotonin re-uptake inhibitors [SSRIs] or tricyclic antidepressants [TCAs]) and major indications. Results: The age- and sex-standardized prevalence was lowest in the two Dutch (391 and 429 users per 10,000 PYs) and highest in the two UK (913 and 936 users per 10,000 PYs) populations in 2008. The prevalence in the Danish, German, and Spanish populations was 637, 618, and 644 users per 10,000 PY respectively. Antidepressants were prescribed most often in 20- to 60-year-olds in the two UK populations compared with the others. SSRIs were prescribed more often than TCAs in all except the German population. In the majority of countries we observed an increasing trend of antidepressant prescribing over time. Two different methods identifying recorded indications yielded different ranges of proportions of patients recorded with the specific indication (15–57 % and 39–69 % for depression respectively). Conclusion: Despite applying uniform methods, variations in the prevalence of antidepressant prescribing were obvious in the different populations. Database characteristics and clinical factors may both explain these variations. Electronic supplementary material

INTRODUCTION

The objectives of drug utilization research have broadened over the years to include economic and quality aspects of medication prescribing and use [1]. Drug utilization studies, published in the 1980s and 1990s, are most often cross-sectional surveys or consist of aggregate country data on drug expenditure or sales volume. The increasing availability of electronic healthcare databases has provided the opportunity for more detailed, longitudinal assessments of drug consumption at a patient level and across healthcare settings, regions, and countries
 Antidepressants are one of the most widely used drug classes, prescribed for a wide range of indications [2] with a reported increasing trend in use [3–14]. Comparison of results of these studies is difficult owing to differences in the methods applied, data sources used, and population groups selected. Cross-country comparisons are few and are made mainly in populations with specific indications or ages [15–19]. The aim of this study was to describe the time trends and the variation in the prevalence of antidepressant prescribing across different European settings applying a uniform method for utilization assessment

MATERIALS AND METHODS

Study setting and population

For this study, information was obtained from seven European electronic healthcare databases: the Spanish BIFAP Project: Database for Pharmacoepidemiological

Research in Primary Care—Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria (www.bifap.org); the German database of the National Association of Statutory Health Insurance Physicians of Bavaria—Kassenärztliche Vereinigung Bayerns (www.kvb.de); the Danish Register of Medicinal Products Statistics, National Institute for Health Data and Disease Control referred to as the Danish national registry in our study (www.ssi.dk); two databases from the United Kingdom: the Clinical Practice Research Datalink (www.cprd.com), and The Health Improvement Network (www.thin-uk.com); and finally, two databases from the Dutch Mondriaan project (www.projectmondriaan.nl): Netherlands Primary Care Research Database (Mondriaan-NPCRD) (www.nivel.nl) and the Almere Health Care group (Mondriaan-AHC)

Most of the databases provide primary care prescribing data. Dispensing data are present in the Danish national registry, the German Bavarian claims, and the Mondriaan AHC (for the latter in addition to prescribing data). Some of the databases include/provide links to secondary care data and registries. The characteristics of these databases have been described in detail elsewhere [20]

Data were obtained for the period between 1 January 2001 and 31 December 2009. The Bavarian claims database was able to provide valid patient information only from 2004 to 2008, while Mondriaan-AHC provided data from 2001 to 2008. Each patient in the databases was considered from the start of the study period or patient's enrolment into a practice/database, or the moment the practice became up to research standard (where applicable), whichever was the latest. Patients were considered in the study population until they left the practice/database or until the end of the study period, whichever came first

Antidepressant prescribing and data analysis

Antidepressant prescribing was defined as patients having a prescription (dispensed in the case of the Danish national registry and claimed in the case of the Bavarian claims database) for a selective serotonin re-uptake inhibitor (SSRI) and/or a tricyclic antidepressant (TCA). Annual period prevalence of antidepressant prescribing was calculated by dividing the number of patients having at least one prescription for an antidepressant in a calendar year by the total number of person-years (PYs) of follow-up in that calendar year in a database during the study period. Because of the dynamic nature of the source population, the denominator was expressed as PYs of follow-up in the given calendar year rather than as persons. Prevalence and 95 % confidence intervals (95 % CI) of overall antidepressants, as well as of SSRIs or TCAs were calculated separately. Prevalence was further stratified by age (10-year bands) and sex. Direct standardization of the overall prevalence with regard to age and sex was performed using the distribution of the Eurostat (http://appsso.eurostat.ec.europa.eu) population in 2008 with 27 countries

Data for the year 2008 (the latest calendar year available in all databases) were stratified according to the number of prescriptions 1, 2–4, 5–9, and ≥10 prescriptions) and recorded indications (on the first prescription) classified into four groups: depression (with or without anxiety/sleep disorders); anxiety disorders (without depression, with or without sleep disorder); and sleeping disorders (without

anxiety and depression). Different coding systems were used in the databases (ICPC for BIFAP and Mondriaan-NCPRD and AHC; ICD-9 in the Bavarian claims and Danish registries and Read codes in CPRD and THIN; protocol published at www.encepp.eu). In the case of missing information, a search was performed within the 3 months before and after the first prescription. An additional analysis was performed by looking for indications recorded any time before (until 1 January 2001) the first prescription

RESULTS

The age- and sex-standardized prevalence of antidepressant prescribing showed a slightly increasing trend between 2001 and 2009 (Fig. 1). The prevalence varied between 359 (Mondriaan-AHC) and 836 (CPRD) patients per 10,000 PYs in 2001 and between 389 (Mondriaan-AHC) and 930 (THIN) patients per 10,000 PYs in 2008. In both UK databases the overall antidepressant use was higher compared with the other databases. The two Dutch Mondriaan databases had lower prevalence in 2008 (376 and 382 patients per 10,000 PYs for Mondriaan-NPCRD and Mondriaan-AHC respectively) compared with the others (Table 1). The two UK databases showed the highest prevalence (917 and 913 users per 10,000 PYs for THIN and CPRD respectively) in 2008 among all (Table 1)

[FIGURE 1] [TABLE 1]

Stratification by sex and age for the year 2008 (Fig. 2) showed (almost two times) higher antidepressant prescribing among female subjects than male subjects in all populations. In general, there was an increase in prevalence with increasing age. The Danish national registry showed a marked increase in prevalence, almost doubling, in age groups from 60–69 years to 80+ years, in both male and female subjects (from 615 to 1,403 and from 1,013 to 2,094 per 10,000 PYs in male and female subjects respectively). Both UK databases showed higher antidepressant prescribing among age groups from 20 through 60 years (more pronounced among female than male subjects) compared with the same age groups in the other databases

[FIGURE. 2]

The prevalence of SSRI prescribing showed a slightly increasing trend between 2001 and 2009 in all except the two Dutch databases, where it remained stable (Fig. 3). The two Dutch and the Bavarian claims databases showed lower prescribing of SSRIs compared with the other databases. Prevalence of TCA prescribing was stable throughout the study period in all databases, but was lower than that of SSRI except in the Bavarian claims database (where TCA prescribing was two times higher than SSRI) (Fig. 3). The Bavarian claims database showed an increasing SSRI and a decreasing TCA trend (237 to 310 and 450 to 391 per 10,000 PYs for SSRI and TCA from 2004 to 2008 respectively). Both UK databases showed higher TCA prescribing in general compared with other databases, except for the Bavarian claims

[FIGURE. 3]

The average number of prescriptions per patient (Table 1) in 2008 varied between 2.3 and 6.4 in SSRI users and between 2.3 and 6.9 in TCA users, with the lowest number of prescriptions per patient in the Bavarian claims database. There were fewer patients with only one SSRI prescription compared with those having only one TCA prescription in 2008 in all databases except in the Danish national registry
 Depression was the most frequently recorded indication in all databases amounting to up 57 % of the patients, as shown in Fig. 4. In CPRD, Mondriaan-AHC and THIN databases depression was recorded for only 23 %, 15 %, and 12 % of patients respectively. In our additional analysis, higher proportions of patients with depression as the registered indication were obtained, ranging from 39 to 69 % of patients

 [FIGURE. 4]

DISCUSSION
This study provides a recent and a distinctive overview of antidepressant prescribing in seven different databases from five European countries assessed according to uniform methods. In the majority of the countries we observed an increasing trend of antidepressant prescribing over time. In particular, there were between-country variations in the prevalence, even after standardization for age and sex. Having applied a uniform method to calculate the prevalence, variations in the results may be evaluated and explained in the light of differences in the database characteristics and/or clinical aspects related to antidepressant use

 Comparability of major findings
Owing to differences in the reported medication class, selected population, utilization measure, and data type in previous studies [10, 16–19, 21–27] no direct comparison with our results can be made. As such, a 40 % increase in antidepressant consumption measured in defined daily doses (DDDs) per 1,000 inhabitants from 2000 to 2004 reported in a Spanish study [28] may reflect changes in duration or dose of treatment rather than an increase in the prevalence of use. The increase in prevalence in the Spanish BIFAP database between 2001 and 2004 was only 14 % in our study
 Our results show that the highest prevalence of antidepressant prescribing was in the UK and the lowest in the Netherlands, with Spain, Denmark, and Germany in between. The standardized (for age and sex) prevalence numbers were not essentially different from the non-standardized ones. Characterization of the denominator of the prevalence ratio in databases with dynamic populations and different protocols for recording patient information can be challenging. An example of such a challenge was present in the German Bavarian claims database, where claims are recorded only on a quarterly basis. In the absence of exact dates of prescriptions and amount of patient-time contributed per patient per year, the denominator of the prevalence ratio could not be optimally defined. Consequently, in calculating PYs of follow-up in the denominator, 1 year of follow-up was assumed for each patient in this database for a given year, instead of the exact amount of time contributed by each patient. This

tends to inflate the denominator and underestimate the prevalence. Therefore, such database differences can influence utilization measures, even though application of uniform definitions is attempted. To test the stability of the denominator in the calculated prevalence, we also computed the prevalence with the denominator as the population number at 1 June of every calendar year in all the databases (data not shown). Results based on this definition of the prevalence ratio were not essentially different from those presented in our study

Sex and age stratification

A distinctive feature in our results was the higher prevalence of prescribing in women compared with men. Moreover, there was a steady increase in the prevalence with increasing age. The characteristic increase in the prevalence in patients aged 70+ years in Denmark has also been reported elsewhere [3, 29, 30]. Older patients in Denmark seem to have higher antidepressant use compared with other European countries, possibly indicating a feature that needs further investigation, as noted previously [30]

An increasing use of antidepressants among adolescents and children under the age of 18 years was reported in two studies in CPRD [31, 32] for the period 1992–2001. In our study we observed a relatively stable trend in the prevalence (94 and 81 users per 10,000 PYs in 2001 and 2009 respectively). A more recent study [33] in THIN (study period 2002–2009) reported a significant drop in SSRI use in 2005; around the time of the advice of the Committee on Safety of Medicines (CSM) on antidepressant prescribing to children and adolescents. We also confirmed this drop in SSRI prescribing in our study (92, 75, and 86 users per 10,000 PYs) in 2001, 2005, and 2009, respectively

A distinctive feature in our results for the UK databases, which has not been reported before, was the remarkable difference (higher) in antidepressant prescribing in the age groups 20 throughout 60 years (especially in female subjects) compared with the same age groups in the other databases. This finding calls for more in-depth investigation of indications for use in this large adult age group in the UK

SSRI versus TCA use

The trend toward a slight increase in SSRI prescribing during the period from 2001 to 2009 reported in our study adds to the knowledge of the widespread use of SSRIs in contrast to the decreasing use of TCAs [34, 35]. The use of SSRIs outweighing that of TCAs has been reported in previous studies [3, 16, 29, 36] and is in line with our findings. The higher use of TCAs compared with SSRIs in Germany found in our study has also been reported in other studies [37, 38]. In a recent study [39], using German statutory claims data for the year 2009, Hoffmann et al. reported that among children and adolescents (aged 12 to 18 years) with a diagnosis of depression, the use of SSRIs was higher than TCA use (55.6 % vs 17.9 %). In our study, we observed a gradual increase (from 30.8 to 42.6 per 10,000 users) and a decrease (from 38.8 to 33.5 per 10,000 users) in the prevalence of SSRI and TCA from 2004 to 2008 respectively in the age group 10–19 years in the Bavarian claims database. Our results suggest the appearance of an increasing trend in SSRI and a decreasing trend in TCA use in Germany, similar to that in other European countries. However, this trend does not confirm the large differences between SSRI and TCA use in the same

age groups, defined without restrictions according to indication (depression), as reported by Hoffmann et al. [39]. Moreover, inclusion of data from specialists, which is the case in the Bavarian claims database, may introduce differences in the prevalence. As shown in a French study [40], TCAs (e.g., amitriptyline or clomipramine) were more frequently prescribed by specialists than by general practitioners. Further analyses are needed to disentangle differences in the prevalence due to prescriber differences, especially because of the somewhat conflicting results reported by a recent Norwegian study on the more frequent prescribing of SSRI as initiation therapy by specialists [41]

Number of prescriptions

The proportion of users with only one prescription in a year is an indicator of a patient subgroup in which treatment is not sustained. This is true unless this single prescription is issued at the end of the calendar year and the patient continues his treatment in the following year. Information on the treatment duration is important for proper comparison of drug use. The definition of a user as a patient with at least one prescription in a year contributes to the measure of the prevalence, while this group does not consist of regular users. Proportions of patients with one prescription reported in our study for Denmark (27 % and 16 % for SSRI and TCA users in 2008 respectively) differ from those reported in another study [3] (22 % and 33 % for SSRI and TCA users in 1995 respectively). This may indicate possible changes in the length of treatment (switching or discontinuation) and not necessarily changes in the prevalence of use

Similarly high proportions of patients with a single prescription, especially of TCA, (in addition to the lowest number of prescriptions in general) in Germany have been reported in another study using a different claims database [38]. Prescribing large packages of antidepressants in Germany (usually for 90 days) and the high percentage of patients stopping or switching their treatment after a single prescription may explain our results. Such differences in prescribing policies should be taken into account when performing country comparisons

Indications

The main clinical indication for antidepressant treatment is depression, which has been reported to be the most frequently reported indication for antidepressant use [2, 36]. Our sensitivity analyses (see Fig. 4) yielded larger proportions (two to fourfold) of patients with recorded indications demonstrating the importance of extensive search criteria. We could not associate the increase in the identified indications with the type of database in our study. Many conditions, such as sleeping and anxiety disorders, are also known to be co-morbidities with depression [42, 43]; hence, a cross-sectional selection of subgroups based on the indication recorded on one prescription may result in miscalssification [44]. The variation in the recording of indications in our study points out that the selection of a population group based on indications may not produce comparable groups in terms of drug use, and therefore hinder direct comparison of utilization patterns

To our knowledge, this is the first study comparing the prevalence of antidepressant prescribing calculated in a uniform manner across different European databases, covering a broad age range, both sexes, major antidepressant groups, and without selection criteria on certain indications. Moreover, the databases are population-based reflecting patient-specific information in contrast to aggregate sales data calculated per inhabitants of a specific region. Owing to the application of common methods for calculating such simple measures, our results reflect the actual features of utilization or changes in treatment course or intensity of prescribing, rather than differences in the methods of calculating the prevalence

A limitation of our study is the inability to reach complete harmonization definitions, which was due to differences in database designs and the heterogeneity of the level of information. Also, no comparisons based on prescribed doses and indications could be performed. Inherent differences in the coding systems used in the databases may also have created differences in capturing indications. Furthermore, no prescriber characteristics analyses were performed. As we mainly had data on prescribing, we were unable to distinguish patients who did not collect their prescriptions. This has been shown to amount to 4 % in the Dutch databases [45]. In addition, some of the differences between countries we observed may be influenced by the availability of individual drugs per country and national prescribing guidelines. A separate study on these specific topics would be informative

CONCLUSION

In conclusion, our study illustrates that harmonizing methods to describe the prevalence of antidepressant prescribing in electronic healthcare databases may contribute to direct cross-country comparisons. Prescribing differences, after the application of a harmonized method, may primarily reflect differences in clinical guidelines among the countries. Direct comparison of results of drug utilization studies may provide a better insight into prescribing practices and hence contribute to better drug safety systems and assessment of future research needs

Electronic supplementary material

Below is the link to the electronic supplementary material

ESM 1(DOCX 11 kb)

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APPENDIX I

For the study of Abbing-Karakahopian et al. "Antidepressant prescribing in five European countries: application of common definitions to assess the prevalence, clinical observations and methodological implications."

List of individual drugs considered in the study

Selective serotonin re-uptake inhibitors (SSRI)
zimeldine
fluoxetine
citalopram
paroxetine
sertraline
alaproclate
fluvoxamine
etoperidone
escitalopram

Tricyclic antidepressants (TCA)
desipramine
imipramine &/oxide
clomipramine
opipramol
trimipramine
lofepramine
dibenzepin
amitriptyline
nortriptyline
protriptyline
doxepin
iprindole
melitracen
butriptyline
dosulepin
amoxapine
dimetacrine
amineptine
maprotiline
quinupramine

TABLES AND FIGURES

Table 1: Antidepressant prescribing in 2008 in seven European healthcare databases

Database/source	BIFAP	Bavarian claims	Danish national registry	CPRD	THIN	Mondriaan-NPCRD	Mondriaan-AHC
Antidepressants							
Patients (n)	94,234	594,745	321,811	397,034	340,798	12,412	5,449
PY in 2008	1,424,572	8,558,315	5,222,891	4,348,431	3,860,850	330,477	142,819
Crude prevalence /10,000 PY (±95 % CI)	662 (657–666)	695 (693–697)	616 (614–618)	913 (910–916)	883 (880–886)	376 (369–382)	382 (372–391)
Standardizedb prevalence /10,000 PY	644	618	637	913	936	429	391
Selective serotonin reuptake inhibitors							
Patientsa (n)	81,020	283,355	280,184	284,922	232,678	8,671	4,101
Prescriptions (n)	512,408	661,607	1,417,063	1,805,959	1,434,894	41,911	26,051
Crude prevalence /10,000 PY (±95 % CI)	569 (565–573)	331 (330–332)	536 (535–538)	655 (653–658)	603 (600–605)	262 (257–268)	287 (278–296)
Standardizedb prevalence /10,000 PY	553	302	556	657	639	271	311
Prescriptions/user (average)	6.3	2.3	5.1	6.3	6.2	4.8	6.4
Users with one prescription (%)	18	37	27	18	22	15	13
Tricyclic antidepressants							

Database/source	BIFAP	Bavarian claims	Danish national registry	CPRD	THIN	Mondriaan-NPCRD	Mondriaan-AHC
Patientsa (n)	16,566	372,656	50,803	133,965	128,696	3,979	1,488
Prescriptions (n)	114,664	843,303	259,209	738,003	734,231	16,381	7,942
Crude prevalence per 10,000 PY (±95 % CI)	116 (115–118)	435 (434-437)	97 (96–98)	308 (306–310)	333 (332–335)	120 (117–124)	104 (99–109)
Standardizedb prevalence /10,000 PY	115	382	99	306	354	128	128
Prescriptions/user (average)	6.9	2.3	5.1	5.5	5.7	4.1	5.3
Users with one prescription (%)	27	45	16	33	34	28	25

PY person-years

aPatients having one or more prescriptions of SSRI/TCA

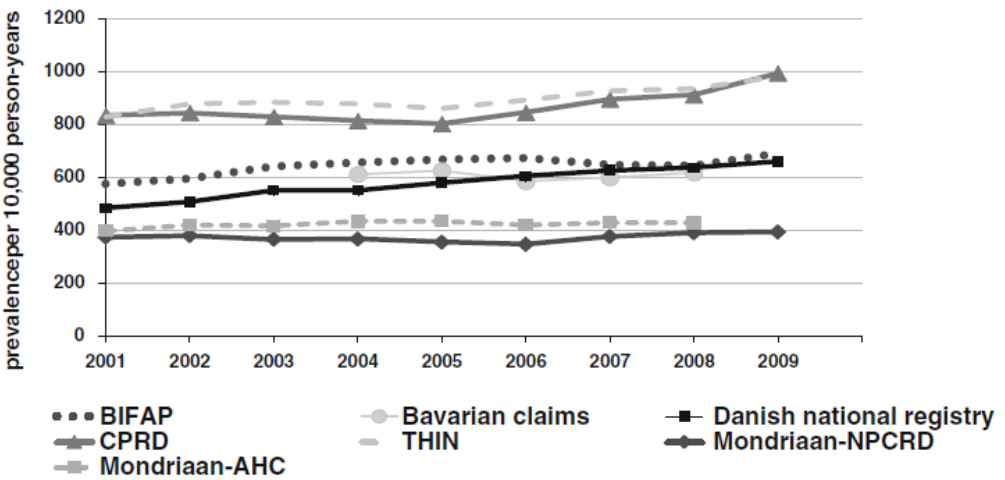bStandardization according to the Eurostat population of 2008

Fig. 1 Age- and sex-standardized 1-year period prevalence of antidepressant prescribing by calendar year in seven European databases from 2001 to 2009

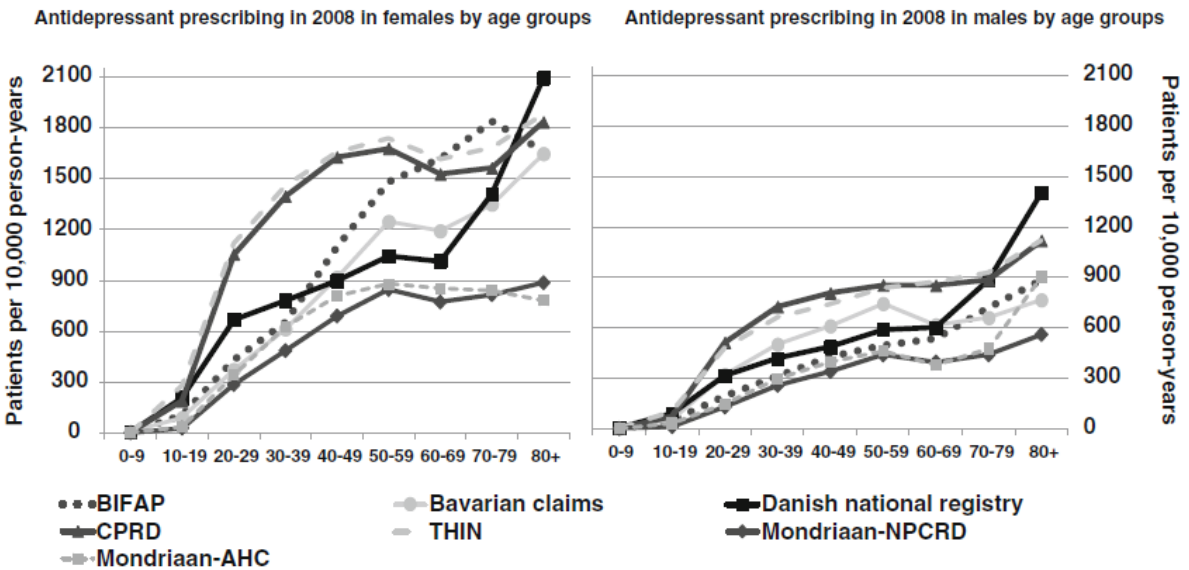**Fig. 2** Period prevalence of antidepressant prescribing in 2008 by sex and age in seven European databases
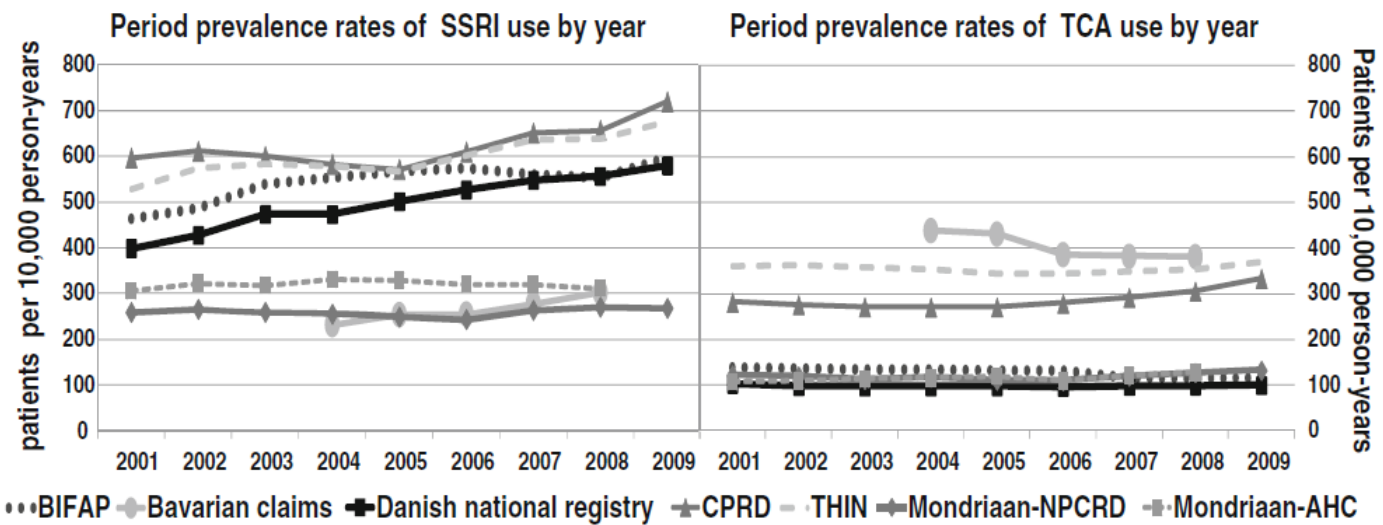

Antidepressant prescribing in 2008 in females by age groups

Antidepressant prescribing in 2008 in males by age groups

- •••• BIFAP
- ◆ CPRD
- ◆ Mondriaan-AHC
- Bavarian claims
- THIN
- Danish national registry
- Mondriaan-NPCRD

Abbing-Karahagopian, V., Huerta, C., Souverein, P.C., Abajo, F. de, Leufkens, H.G.M., Slattery, J., Alvarez, Y., Miret, M., Gil, M., Oliva, B., Hesse, U., Requena, G., Vries, F. de, Rottenkolber, M., Schmiedl, S., Reynolds, R., Schlienger, R.G., Groot, M.C.H. de, Klungel, O.H., Staa, T.P. van, Dijk, L. van, Egberts, A.C.G., Gardarsdottir, H., Bruin, M.L. de. Antidepressant prescribing in seven European countries: application of common definitions to assess the prevalence, clinical observations, and methodological implications. European Journal of Clinical Pharmacology: 2014

Fig. 3 Age- and sex-standardized prevalence of SSRI and TCA prescribing in seven European healthcare databases from 2001 to 2009
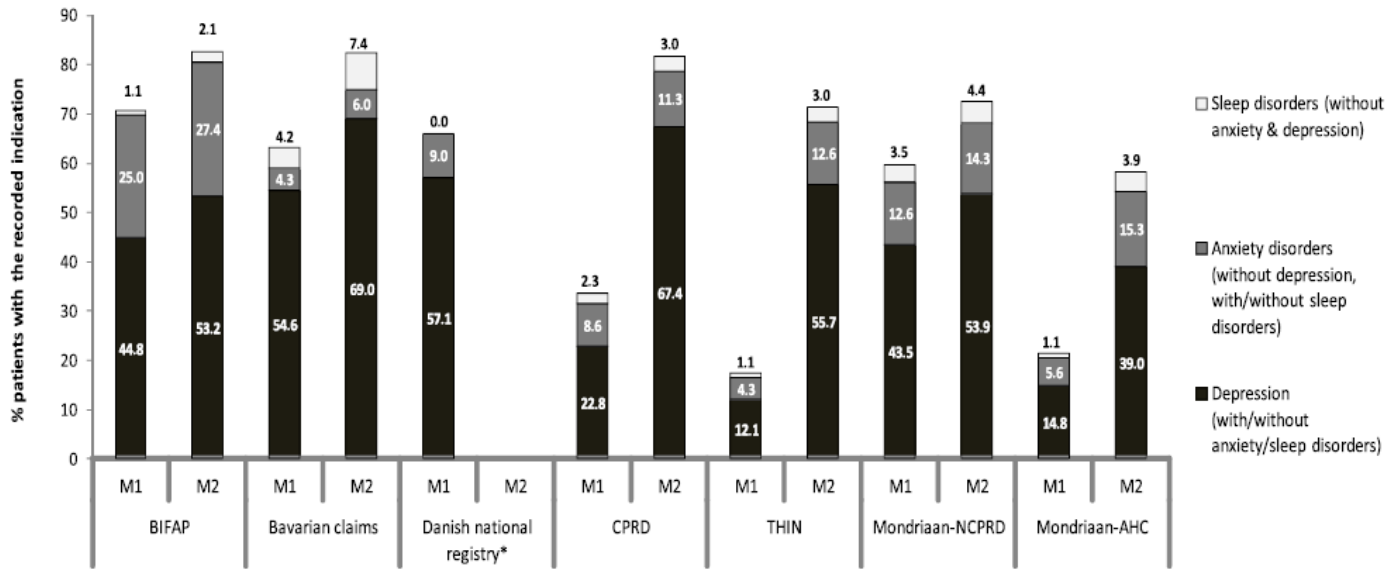
Fig. 4 Distribution of the recorded indications for antidepressants assessed using two different methods in seven European healthcare databases in 2008. M1=indication assessed in the period 3 months before/after the first antidepressant prescription in 2008. M2=indication assessed in the period from the first antidepressant prescription in 2008 going backwards until 1 January 2001 (1 January 2004 in the Bavarian claims) *Asterisk* Assessment of the M2 method in the Danish national registry was not possible