How often are antidepressants prescribed off-label among older adults in Germany? A claims data analysis

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Aim: To estimate the extent of off-label prescribing of antidepressants in older adults and to characterize patients with off-label vs on-label prescriptions of antidepressants using a large German health claims database.

Methods: Using data from the German Pharmacoepidemiological Research Database (GePaRD), we conducted a cross-sectional study in adults aged 65 years or older with a dispensation of an antidepressant between 1 January 2009 and 31 December 2015 after a period of 365 days without such a dispensation. We assessed the overall and annual proportion of off-label prescriptions of antidepressants by class and individual substance.

Results: Among 263,276 incident users of antidepressants, the proportion of off-label prescribing was 43.6% (95% CI 43.4-43.8%) with little variation between 2009 and 2015 (42.2-44.4%). The proportion of off-label use was higher in men (49%) than women (41%). While the proportion of off-label prescriptions was highest for tri- and tetracyclic antidepressants with 56.2% (amitriptyline 54.6%, maximum 65.9% for trimipramine), it amounted to 41.8% for selective serotonin reuptake inhibitors (citalopram 41.6%, maximum 46.0% for escitalopram) and was 51.2% for mirtazapine. Indicators of overall morbidity were similar in both groups, eg, pain was coded in 72% of off-label users vs 77% of on-label users (insomnia 20% vs 24%).

Conclusion: Our study suggests a high prevalence of off-label antidepressant use among older adults in Germany, which was not restricted to certain classes of antidepressants or individual antidepressants. Given the unclear risk-benefit ratio, studies investigating the safety of off-label use among older adults for individual antidepressants are urgently needed.

KEYWORDS
administrative claims, antidepressants, off-label use, older adults

INTRODUCTION

The prevalence of antidepressant use has increased over the past decades.¹ It has been suspected that the increase in antidepressant use is partly due to prescriptions for indications such as insomnia or pain, for which many antidepressants are not approved by marketing authorities.² This kind of prescription is typically called off-label use.³–⁵ A broader definition of off-label use also includes prescriptions disregarding age-related restrictions or the presence of contraindications.⁶ In general, off-label use of drugs is subject to more uncertainties regarding the risk-benefit ratio compared to on-label use as the safety of the drug with respect to the off-label

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use has typically not or not sufficiently been studied in clinical trials.3,7,8

While several studies have investigated the extent of off-label antidepressant use in children,9–11 only few have focused on adults,5 particularly older adults.12,13 Especially in older adults, there may be increasing prevalence of off-label use, eg, due to insomnia or other health conditions relevant to this age group. To overcome this research gap, there is no optimal data source but various approaches may complement each other. A German study including 3117 older adults (mean age 70 years) used primary data,13 where recall bias regarding drug exposure14,15 and selection bias are typical challenges and also sample size is usually lower compared to studies using healthcare databases such as claims data. Another study including 3692 US veteran nursing home patients aged 65 or older used primary data linked to dispensation data.12 Neither study provided results stratified by individual antidepressant (active substance). Instead, one stratified only by class12 and the other by any antidepressant use.13 Nor did they provide information on the specialty of the prescribing physicians, which would be useful to investigate patterns of care in this context. Compared to the data sources used in those studies, the particular strengths of claims data are the absence of recall and volunteer bias, the large sample size allowing detailed analyses stratified by individual antidepressants and the availability of information on the specialty of the prescribing physician. Although most claims databases lack direct information on indications, they contain diagnosis codes allowing indirect estimation of whether antidepressants were used on- or off-label.

In the light of these arguments, we aimed to estimate the extent of off-label prescribing of antidepressants in older adults overall and for individual antidepressants, and to characterise patients with off-label vs on-label prescriptions of antidepressants using a large German claims database.

2 | METHODS

2.1 | Database

We used the German Pharmacoepidemiological Research Database (GePaRD) for this study, which is based on claims data from four statutory health insurance providers in Germany and currently includes information on approximately 25 million persons who have been insured with one of the participating providers since 2004. In addition to demographic data, GePaRD contains information on drug dispensations as well as outpatient (ie, from general practitioners and specialists including outpatient psychiatric clinics) and inpatient services and diagnoses. Per data year, there is information on approximately 17% of the general population and all geographical regions of Germany are represented.16 In Germany, the utilization of health insurance data for scientific research is regulated by the Code of Social Law. All involved health insurance providers as well as the German Federal (Social) Insurance Office and the Senator for Science, Health, and Consumer Protection in Bremen as their responsible authorities approved the use of GePaRD data for this study. Informed consent for studies based on GePaRD is not required by law and according to the Ethics Committee of the University of Bremen these studies are exempt from institutional review board review.

In GePaRD, diagnosis codes are registered according to the International Classification of Diseases 10th revision, German modification (ICD-10-GM) in the in- and outpatient setting. In the outpatient setting, physicians are expected to code the disease(s) for which they treat their patients and thus the indications for drugs17 once per quarter.17,18 Outpatient diagnosis codes are available on a quarterly basis, while an exact date is available for outpatient visits. In the case of only one outpatient visit per quarter, the diagnosis can be assigned to that visit. Furthermore, the additional coding of diagnostic certainty is mandatory in the outpatient setting in Germany. This coding differentiates between “confirmed”, “suspected”, “status post” and “excluded” diagnoses. Drugs can be identified by the respective Anatomical Therapeutic Chemical (ATC) code.

2.2 | Study population

For this study, data from 2008 to 2015 were used. We included persons aged 65 years or older with a prescription of antidepressants in 2009 or later after a 1-year preobservation period without dispensation of antidepressants. The day of the dispensation of the first antidepressant in this period was defined as the index day. Persons not continuously insured for at least 365 days before the
index day were excluded. Antidepressants were identified based on the ATC code N06A. We excluded ometramol (N06AA05) and tryptophan (N06AX02) because, though classified as antidepressants in the ATC-system, depression is not an approved indication for these drugs in Germany. Persons were excluded if the prescription of more than one antidepressant on the same day led to cohort entry. In those cases, allocation to on- vs off-label use might not have been clear given that indications partly differ between antidepressants. This also applies to the prescription of multiple antidepressants with the same ATC code, as different forms of application might have divergent indications.

2.3 | Definition and assessment of off-label use

In accordance with other studies,3–5 we defined off-label use as the prescription of an antidepressant to persons that do not have the diseases indicated in the summary of product characteristics. Additionally, we considered age restrictions for reboxetine and agomelatine (ATC codes N06AX18 and N06AX22), which are contraindicated in patients above the age of 64 and 74 years, respectively.19,20

We used two different methods to assign indications for which specific antidepressants are approved: (i) based on the most recent indications of the original product (ie, these indications were also assigned to generic products containing the same active substance) and (ii) based on the indications of the specific product according to the summary of product characteristics (see Supporting Information Table S1). We used method (i) for the main analysis and conducted sensitivity analyses based on method (ii).

To estimate whether a prescription was off- or on-label, we searched for outpatient diagnosis codes corresponding to the indication(s) of the respective antidepressant in the 365 days before the index day (the respective codes may be found in Supporting Information Table S1). We only considered diagnosis codes labelled as “confirmed”. In a sensitivity analysis, we additionally considered all outpatient diagnoses coded in the full quarter of the index day and in the following quarter. We considered only outpatient diagnoses because outpatient dispensations usually follow the consultation of a physician in the outpatient setting. As mentioned before, physicians are expected to code the disease(s) for which they treat patients and thus prescribe drugs. This also applies to persons newly discharged from hospital who received a list of medication to use post-hospitalisation, as hospitals in Germany are not entitled to prescribe drugs for direct reimbursement by the statutory health insurances during our study period.21

Given our intention to provide a conservative estimate of the overall proportion of off-label use and the fact that coding in the outpatient setting may tend to be unpecific, we included a broader spectrum of ICD-10-GM codes in the definition of depression for the overall estimate. For example, we also included a code for mixed anxiety and depressive disorder (F43.2) and a code for adjustment disorders (F41.2).

2.4 | Characterisation of persons with on- and off-label use of antidepressants

In a first step, we characterised the persons classified as on- vs off-label users of antidepressants with respect to age, sex and general comorbidity using the Charlson Comorbidity Index,22 the overall number of hospitalisations in the year before cohort entry and the number of different medications dispensed in the 182 days before cohort entry. We also assessed the specialty of the physician prescribing the index antidepressant.

To characterise persons with off-label use of antidepressants regarding health conditions that might explain antidepressant use in these persons, we first compiled a list of codes for diseases and other characteristics (eg, palliative care) that could lead to off-label prescribing of antidepressants (see Supporting Information Table S2). We also considered codes for medication used to treat the selected diseases as this provides another layer of information on these conditions. We searched for the codes for diseases and characteristics in the 365 days preceding cohort entry, and for medication in the 182 days before cohort entry, respectively. For comparison, we also searched for these codes in persons classified as on-label users.

2.5 | Data analysis

The proportion of off-label users was calculated by dividing the number of incident antidepressant users classified as off-label users (nominator) by the number of all incident antidepressant users (denominator). We calculated this proportion for the whole study population and stratified by year of index date. The nominator was determined based on methods (i) and (ii), respectively. We calculated 95% confidence intervals (CIs) using the Wilson method. In addition to calculating the overall proportion of off-label antidepressant users we also determined the proportion of off-label users for the different classes of antidepressants and for the individual antidepressants. All analyses were performed using SAS version 9.4.

2.6 | Patient and public involvement statement

This study was conducted without patient involvement. However, we plan to disseminate the results of the study to the relevant public and professional audience using multiple communication pathways. The results of this study illustrate the need for interventional studies at the prescriber level where it will be important to take the patients’ perspectives into account.

2.7 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to
3 | RESULTS

Overall, we included 263,276 incident users of antidepressants. Table 1 provides information on the distribution of the age, sex, indicators of comorbidity and speciality of the physician prescribing the index antidepressant for all included persons and stratified by on- vs off-label users of antidepressants. Median age was 73 years (interquartile range 69 to 79) and 33% of users were male.

According to the Charlson Comorbidity Index, the overall disease burden was low to moderate in three quarters of included persons (39% with a score of 0 to 2 and 37% with a score of 3 to 5). Almost half of all persons used seven or more different drugs in the 6 months before cohort entry and more than half were hospitalised at least once in the pre-observation period. The index antidepressant was most frequently prescribed by a general practitioner (73%). The proportion of males was seven percentage points higher compared to off-label users, while the indicators of comorbidity were similarly distributed. The index drug was less frequently prescribed by a psychiatrist or psychotherapist in off-label users compared to on-label users (9% vs 15%).

### TABLE 1 Characteristics of incident antidepressant users included in this study

|                                | Total (n = 263,276) | Off-label users (n = 114,923) | On-label users (n = 148,353) |
|--------------------------------|---------------------|-------------------------------|-----------------------------|
| Age at index day                |                     |                               |                             |
| 65-69 (n, %)                   | 77,436 (29.4)       | 31,022 (27.0)                 | 46,414 (31.3)               |
| 70-74 (n, %)                   | 70,757 (26.9)       | 31,463 (27.4)                 | 39,294 (26.5)               |
| 75-79 (n, %)                   | 50,170 (19.1)       | 22,293 (19.4)                 | 27,877 (18.8)               |
| 80-84 (n, %)                   | 35,624 (13.5)       | 16,155 (14.1)                 | 19,469 (13.1)               |
| 85-89 (n, %)                   | 21,692 (8.2)        | 10,254 (8.9)                  | 11,438 (7.7)                |
| ≥90 (n, %)                     | 7,597 (2.9)         | 3,736 (3.2)                   | 3,861 (2.6)                 |
| Mean (standard deviation)      | 74.6 (7.09)         | 74.9 (7.10)                   | 74.2 (7.00)                 |
| Median (interquartile range)   | 73 (69-79)          | 74 (69-80)                    | 73 (68-79)                  |
| Sex                            |                     |                               |                             |
| Female (n, %)                  | 176,972 (67.2)      | 72,833 (63.4)                 | 104,139 (70.2)              |
| Charlson Comorbidity Indexa    |                     |                               |                             |
| 0-2 (n, %)                     | 101,392 (38.5)      | 44,496 (38.7)                 | 56,896 (38.4)               |
| 3-5 (n, %)                     | 97,787 (37.1)       | 42,216 (36.7)                 | 55,571 (37.5)               |
| ≥6 (n, %)                      | 64,097 (24.3)       | 28,211 (24.5)                 | 35,886 (24.2)               |
| Number of different medications used in the 182 days before cohort entry |                     |                               |                             |
| 0 (n, %)                       | 9,564 (3.6)         | 4,107 (3.6)                   | 5,457 (3.7)                 |
| 1-3 (n, %)                     | 55,459 (21.1)       | 23,972 (20.9)                 | 31,487 (21.2)               |
| 4-6 (n, %)                     | 73,038 (27.7)       | 31,970 (27.8)                 | 41,068 (27.7)               |
| 7-9 (n, %)                     | 57,320 (21.8)       | 25,106 (21.8)                 | 32,214 (21.7)               |
| ≥10 (n, %)                     | 67,895 (25.8)       | 29,768 (25.9)                 | 38,127 (25.7)               |
| Mean (standard deviation)      | 7.0 (4.79)          | 7.1 (4.80)                    | 7.0 (4.80)                  |
| Median (interquartile range)   | 6 (4-10)            | 6 (4-10)                      | 6 (4-10)                    |
| Number of hospitalisations in the year before cohort entry |                     |                               |                             |
| 0 (n, %)                       | 125,361 (47.6)      | 54,868 (47.7)                 | 70,493 (47.5)               |
| 1-3 (n, %)                     | 120,313 (45.7)      | 52,483 (45.7)                 | 67,830 (45.7)               |
| 4-6 (n, %)                     | 14,584 (5.5)        | 6197 (5.4)                    | 8387 (5.7)                  |
| 7-9 (n, %)                     | 2171 (0.8)          | 972 (0.8)                     | 1199 (0.8)                  |
| ≥10 (n, %)                     | 847 (0.3)           | 403 (0.4)                     | 444 (0.3)                   |
| Speciality of the prescribing physiciana |                     |                               |                             |
| General practitioner (n, %)    | 192,753 (73.2)      | 86,280 (75.1)                 | 106,473 (71.8)              |
| Psychiatrist, psychotherapist (n, %) | 32,259 (12.3) | 10,703 (9.3)                  | 21,556 (14.5)               |
| Specialist care: other (n, %)  | 37,683 (14.3)       | 17,633 (15.4)                 | 20,020 (13.5)               |

*aFor 581 included persons (0.2% of all), the specialty of the prescribing physician could not be assessed.*
The overall proportion of off-label use was 44% (95% CI 43-44%) with a variation of about two percentage points or less between 2009 and 2015 (minimum 42%, maximum 44%). When applying method (ii), off-label use was 2-3% higher compared to method (i) (see Figure 1 and Supporting Information Table S3).

The proportion of off-label use was higher in men (49%, 48-49%) than in women (41%, 41-41%), with a variation of about three percentage points or less between 2009 and 2015 in both sexes (see Figure 2 and Supporting Information Tables S4 and S5). With rising age, the proportion of off-label use increased. In patients aged 65-69 years, 40% of all prescriptions were off-label; this increased to 45% in patients aged 80-84 years and to 49% at an age of 90 years or older, as shown in Figure 2.

The proportion of off-label use varied between classes and also between active substances within classes (see Table 2). At the class level, it was highest for tri- and tetracyclic antidepressants (TCAs), where it amounted to 56%. Among TCAs the proportion of off-label use was highest for trimipramine (66%) and it was 55% for amitriptyline, the most often prescribed antidepressant. Among selective serotonin reuptake inhibitors (SSRIs) the overall proportion of off-label use was 42%; this was similar to the proportion observed for citalopram, the most widely used substance in this class, while the maximum in this class was observed for escitalopram (46%). Between the two selective serotonin noradrenaline reuptake inhibitors (SSNRIs), there was a difference of 11 percentage points in the proportion of off-label use; it was 49% for duloxetine and 38% for venlafaxine. For mirtazapine, the second most often prescribed antidepressant, the proportion of off-label use was 51%. In the sensitivity analyses using method (ii) to define off-label use, the proportion of off-label prescriptions was often similar to the base-case analyses or slightly higher, with the difference being mostly below five percentage points. The proportion of off-label use increased by more than 10 percentage points in the sensitivity analyses only for amitriptyline (11 percentage points) and for St John's wort (26 percentage points).

In sensitivity analysis considering not only diagnoses in the 365 days before the index prescription, but also in the quarter after the index prescription, the overall proportion of off-label use decreased by about 4 percentage points (40%, 40-40%), (see Supporting Information Table S6).

With the exception of depression, the prevalences of diagnoses that are indications of some antidepressants were similar in off- and on-label users or lower in off-label users, as shown in Table 3. For example, pain was coded in 72% of off-label users vs 77% of on-label users (anxiety 6% vs 16%, insomnia 20% vs 24%). For other diagnoses that could be associated with off-label use as well as for related medications, the prevalences were either similar in both groups or the difference was three percentage points or lower.

4 | DISCUSSION

4.1 | Principal findings

The aim of our study was to quantify off-label use of antidepressants in the elderly German population using claims data and to describe characteristics of patients with off-label prescriptions of antidepressants compared to on-label users. Including more than 250 000 older adults initiating antidepressant use in Germany, our study suggests that about 44% of antidepressants were prescribed off-label. This proportion remained stable between 2009 and 2015, was higher in men (49%) compared to women (41%) and increased with age (40% in age group 60-64 vs 45% in age group 80-84). While the proportion of off-label prescriptions was highest for TCAs (56%, maximum 66% for trimipramine), it amounted to 42% for SSRIs (maximum 46% for escitalopram). Similar to on-label users, there was a diagnosis of pain for more than 70% of off-label users and of insomnia for about 20% of them. The prevalences of co-morbidities/co-medications were also similar between the groups.
4.2 Comparison with other studies

Despite the relevance of the topic, studies on off-label prescribing of antidepressants in the adult population are scarce, particularly those with a focus on older adults.\textsuperscript{12,13} The proportion of overall off-label use observed in our study was similar to the proportion of overuse (defined as antidepressant use without depression or other clinical indications) reported by Boehlen et al (44% vs 42%) based on a study among 3117 older adults in Germany, including 230 persons treated with antidepressants.\textsuperscript{13} Also Hanlon et al reported that 42% of US veterans without depression were prescribed one or more antidepressants.\textsuperscript{12} Although off-label use and overuse are not exactly the same, this agreement is remarkable given the differences in study designs and types of data used.\textsuperscript{12,13} Boehlen et al reported a higher proportion of overuse among males, which is similar to the pattern observed in our study for off-label use,\textsuperscript{13} while a survey from Sweden suggested a higher proportion of overtreatment among older women compared to older men.\textsuperscript{31}

Boehlen et al did not provide information on overuse according to class of antidepressant or individual antidepressants, most likely due to the limited sample size (96 persons in the group "overuse").\textsuperscript{13} Hanlon et al reported a higher proportion of off-label use for TCAs (73%) compared to SSRIs (60%), similar to our study, but the overall frequency of TCA prescriptions was much lower compared to our study. Of all antidepressant prescriptions, the proportion of TCAs was 6% in the study by Hanlon et al vs 41% in our study.

To compare our results on off-label use for individual antidepressants to other studies, we considered the study by Wong et al conducted in the general adult population because there was no study providing this information specifically for older adults.\textsuperscript{5} They used data from an electronic prescription and drug management system in the primary care setting in Canada and also reported a higher prevalence of off-label prescriptions for TCAs than for SSRIs. Similar to our study they found a high prevalence of off-label use for amitriptyline, even higher than in our study (93% vs 55%). They also found a high prevalence of off-label use for trazodone (89%), which was again higher than in our study (55%). Interestingly, of all antidepressant prescriptions the proportion of trazodone was 9% in the study by Wong et al vs 0.3% in our study. For venlafaxine, the proportion of off-label use was only 7% in the study by Wong et al as opposed to 38% in our study. Again, the overall proportion of venlafaxine prescriptions was rather different between studies (20% of all antidepressant prescriptions in the study by Wong et al vs 2% in our study).\textsuperscript{5} These examples suggest that at the level of the individual antidepressant, the patterns regarding off-label use and also the overall prescribing patterns are rather different between age groups and settings.

4.3 Possible explanations and implications

Our findings regarding diagnoses and conditions coded among off-label users (70% with pain, 20% with insomnia) suggest that most patients receiving off-label antidepressants have diagnoses for which only some antidepressants are approved, for example doxepine is indicated for the treatment of insomnia\textsuperscript{32} and trimipramine is licensed for the treatment of depression with insomnia as a prevailing symptom. Other antidepressants are not licensed for insomnia, but some TCAs (including trazodone and trimipramine) are known to have sedative properties already at dosages lower than those used for the treatment of depression.\textsuperscript{33} With respect to the treatment of pain, certain antidepressants such as the TCAs amitriptyline, clomipramine, doxepine and imipramine, and the SSNRI duloxetine are licensed for this
### TABLE 2  Proportion of off-label use by class of antidepressant and active substance

| Antidepressant used (n, %) | Proportion off-label (95% CI) | Method (i) | Method (ii) |
|---------------------------|-------------------------------|------------|-------------|
| Any (263 276, 100.0%)     | 43.6% (43.4-43.8)             | 46.2% (46.0-46.4) | |
| TCA (107 711, 40.9%)      | 56.2% (55.9-56.5)             | 62.5% (62.2-62.8) | |
| - Amitriptyline\(e\) (61 832, 23.5%) | 54.6% (54.2-55.0)         | 66.0% (65.6-66.4) | |
| - Doxepin (22 125, 8.4%)  | 51.9% (51.2-52.5)             | 50.7% (50.0-51.3) | |
| - Trimipramine (21 611, 8.2%) | 65.9% (65.3-66.5)       | 65.9% (65.3-66.5) | |
| - Clomipramine (668, 0.3%) | 45.8% (42.1-49.6)         | 47.2% (43.4-51.0) | |
| - Maprotiline (540, 0.2%)  | 43.3% (39.2-47.6)             | 43.3% (39.2-47.6) | |
| - Nortriptyline (446, 0.2%) | 59.9% (55.3-64.3)         | 54.5% (49.8-59.1) | |
| - Imipramine (483, 0.2%)   | 41.1% (30.5-52.6)             | 45.2% (34.3-56.6) | |
| - Desipramine (3, 0.0%)    | 33.3% (6.2-79.2)             | 33.3% (6.2-79.2) | |
| - Dosulepin (3, 0.0%)      | 33.3% (6.2-79.2)             | 33.3% (6.2-79.2) | |
| SSRI (70 751, 26.9%)      | 41.8% (41.5-42.2)             | 42.9% (42.5-43.3) | |
| - Citalopram (53 883, 20.5%) | 41.6% (41.2-42.0)         | 43.0% (42.5-43.4) | |
| - Sertraline (6359, 2.4%)  | 42.1% (40.9-43.4)             | 43.7% (42.5-44.9) | |
| - Escitalopram (5383, 2.0%) | 46.0% (44.7-47.4)         | 43.6% (42.3-44.9) | |
| - Paroxetine (2668, 1.0%)  | 40.3% (38.5-42.2)             | 41.1% (39.3-43.0) | |
| - Fluoxetine (2385, 0.9%)  | 39.5% (37.5-41.4)             | 39.6% (37.7-41.6) | |
| - Fluvoxamine (73, 0.0%)   | 41.1% (30.5-52.6)             | 45.2% (34.3-56.6) | |
| NASSA (58 683, 22.3%)     | 51.1% (50.7-51.5)             | 52.4% (52.0-52.8) | |
| - Mianserin (248, 0.1%)    | 45.2% (39.1-51.4)             | 45.2% (39.1-51.4) | |
| - Mirtazapine (58 435, 22.2%) | 51.2% (50.8-51.6)       | 52.4% (52.0-52.8) | |
| SSNRI (12 417, 4.7%)      | 44.2% (43.3-45.1)             | 46.9% (46.0-47.8) | |
| - Duloxetine (7152, 2.7%)  | 48.7% (47.5-49.8)             | 51.8% (50.7-53.0) | |
| - Venlafaxine (5265, 2.0%) | 38.2% (36.9-39.5)             | 40.2% (38.9-41.5) | |
| Herbal and homeopathic (1989, 3.8%) | 30.6% (29.7-31.5)   | 55.8% (54.8-56.7) | |
| - Hypericum/St John's Wort (9733, 3.7%) | 30.3% (29.4-31.3) | 56.0% (55.0-57.0) | |
| - Homoeopathic antidepressants (156, 0.1%) | 44.2% (36.7-52.1) | 39.7% (32.4-47.6) | |
| MAO (303, 0.1%)            | 37.6% (32.4-43.2)             | 40.3% (34.9-45.9) | |
| - Moclobemide (272, 0.1%)  | 38.6% (33.0-44.5)             | 41.5% (35.9-47.5) | |
| - Translycypromine (31, 0.0%) | 29.0% (16.1-46.6)   | 29.0% (16.1-46.6) | |
| NARI (249, 0.1%)           | 100% (98.5-100)              | 100% (98.5-100) | |
| - Reboxetine\(e\) (249, 0.1%) | 100% (98.5-100)        | 100% (98.5-100) | |
| Other (3273, 1.2%)         | 55.2% (53.5-56.9)             | 55.2% (53.5-56.9) | |
| - Agomelatine (2000, 0.8%) | 58.5% (56.3-60.6)             | 58.5% (56.3-60.6) | |
| - Agomelatine, users <75 years\(f\) (1311, 0.5%) | 36.6% (34.1-39.3) | 36.7% (34.1-39.3) | |
| - Trazodone (900, 0.3%)    | 55.3% (52.1-58.6)             | 55.3% (52.1-58.6) | |
| - Bupropion (259, 0.1%)    | 40.5% (34.7-46.6)             | 40.5% (34.7-46.6) | |
| - Tianeptine (88, 0.0%)    | 28.4% (20.0-38.6)             | 28.4% (20.0-38.6) | |
| - Vortioxetin (26, 0.0%)   | 34.6% (19.4-53.8)             | 34.6% (19.4-53.8) | |

TCA, tri- and tetracyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; MAO, monoamine oxidase inhibitor; NARI, noradrenaline reuptake inhibitor; SSNRI, selective serotonin noradrenaline reuptake inhibitor; NASSA, noradrenergic and specific serotoninergic antidepressant

\(e\)Method (i) was used in the base-case analyses; it defines off-label use by the indications of the active substance.

\(f\)Method (ii) was used in the sensitivity analyses; it defines off-label use by the indications of the preparation.

\(f\)Additionally considering ICD-10-GM codes F41.2 and F43.2 for depression as indication.

\(e\)Amitriptyline is included here.

\(e\)The proportion is 100% as the use of reboxetine is contraindicated above the age of 64.

\(e\)Agomelatine is contraindicated in patients aged 75 years or older.
### Table 3: Distribution of factors potentially associated with off-label prescribing in antidepressant users

| Diagnosis (assessed in the year before cohort entry) | Total (n = 263,276) | Off-label users (n = 114,923) | On-label users (n = 148,353) |
|----------------------------------------------------|---------------------|--------------------------------|-----------------------------|
| **Diagnoses other than depression that are indications for some antidepressants** | | | |
| Pain                                               | 197,714 (75.1)      | 82,784 (72.0)                  | 114,930 (77.5)              |
| Insomnia                                           | 58,604 (22.3)       | 23,020 (20.0)                  | 35,584 (24.0)               |
| Anxiety                                            | 30,911 (11.7)       | 6,563 (5.7)                    | 24,348 (16.4)               |
| Alcohol abuse                                      | 14,091 (5.4)        | 5,554 (4.8)                    | 8,537 (5.8)                 |
| Diabetic polyneuropathy                            | 9,472 (3.6)         | 3,692 (3.2)                    | 5,780 (3.9)                 |
| Drug abuse                                         | 7,782 (3.0)         | 2,504 (2.2)                    | 5,278 (3.6)                 |
| Bipolar disorders                                  | 1,737 (0.7)         | 409 (0.4)                      | 1,328 (0.9)                 |
| Obsessive compulsive disorder                      | 632 (0.2)           | 129 (0.1)                      | 503 (0.3)                   |
| **Diagnoses potentially associated with off-label prescription of antidepressants** | | | |
| Diabetes                                           | 90,518 (34.4)       | 39,609 (34.5)                  | 50,909 (34.3)               |
| Non-metastatic cancer                              | 55,267 (21.0)       | 24,651 (21.5)                  | 30,616 (20.6)               |
| Ischemic stroke                                    | 36,107 (13.7)       | 16,255 (14.1)                  | 19,852 (13.4)               |
| Dementia                                           | 29,073 (11.0)       | 13,256 (11.5)                  | 15,817 (10.7)               |
| Metastatic cancer                                  | 14,305 (5.4)        | 6,864 (6.0)                    | 7,441 (5.0)                 |
| Parkinson's disease                                | 11,751 (4.5)        | 4,891 (4.3)                    | 6,860 (4.6)                 |
| Migraines                                          | 11,394 (4.3)        | 4,150 (3.6)                    | 7,244 (4.9)                 |
| Fibromyalgia                                       | 3,383 (1.3)         | 1,096 (1.0)                    | 2,287 (1.5)                 |
| Schizophrenia                                      | 1,569 (0.6)         | 646 (0.6)                      | 923 (0.6)                   |
| Multiple sclerosis                                  | 994 (0.4)           | 363 (0.3)                      | 631 (0.4)                   |
| **Comorbidities (assessed in the year before cohort entry)** | | | |
| Hypertension                                       | 224,096 (85.1)      | 98,088 (85.4)                  | 126,008 (84.9)              |
| COPD                                               | 132,156 (50.2)      | 56,041 (48.8)                  | 76,115 (51.3)               |
| Cardiac arrhythmia                                 | 115,306 (43.8)      | 49,277 (42.9)                  | 66,029 (44.5)               |
| Coronary heart disease                             | 112,400 (42.7)      | 48,922 (42.6)                  | 63,478 (42.8)               |
| Cerebrovascular diseases                           | 91,721 (34.8)       | 39,423 (34.3)                  | 52,298 (35.3)               |
| Liver diseases                                     | 74,628 (28.3)       | 31,167 (27.1)                  | 43,461 (29.3)               |
| Renal failure                                      | 57,323 (21.8)       | 25,484 (22.2)                  | 31,839 (21.5)               |
| Macular degeneration                               | 28,752 (10.9)       | 12,260 (10.7)                  | 16,492 (11.1)               |
| Movement disorders                                 | 28,640 (10.9)       | 11,496 (10.0)                  | 17,144 (11.6)               |
| Psychoses                                          | 9,831 (3.7)         | 3,845 (3.3)                    | 5,986 (4.0)                 |
| Delirium                                           | 6,630 (2.5)         | 3,141 (2.7)                    | 3,489 (2.4)                 |
| Cystic fibrosis                                    | 33 (0.0)            | 19 (0.0)                       | 14 (0.0)                    |
| **Medication (used in the 182 days before cohort entry)** | | | |
| Drugs for respiratory diseases                     | 81,126 (30.8)       | 35,005 (30.5)                  | 46,121 (31.1)               |
| Opioids                                            | 51,997 (19.7)       | 22,335 (19.4)                  | 29,662 (20.0)               |
| Antidiabetic drugs                                 | 41,926 (15.9)       | 18,868 (16.4)                  | 23,058 (15.5)               |
| Anxiolytics                                        | 25,717 (9.8)        | 9,158 (8.0)                    | 16,559 (11.2)               |
| Hypnotics and sedative drugs                       | 23,189 (8.8)        | 9,593 (8.3)                    | 13,596 (9.2)                |
| Antiparkinsonian drugs                             | 22,378 (8.5)        | 9,455 (8.2)                    | 12,923 (8.7)                |
| Insulin                                            | 18,202 (6.9)        | 8,329 (7.2)                    | 9,873 (6.7)                 |
| Atypical antipsychotics                            | 17,041 (6.5)        | 6,568 (5.7)                    | 10,473 (7.1)                |
| Antineoplastic drugs                               | 14,148 (5.4)        | 6,385 (5.6)                    | 7,763 (5.2)                 |
| Antidepressive drugs                               | 13,790 (5.2)        | 6,667 (5.8)                    | 7,123 (4.8)                 |
| Lithium                                            | 11,811 (0.4)        | 172 (0.1)                      | 10,639 (0.7)                |

(Continues)
indication. When treating insomnia or pain, physicians may tend to assume that antidepressants in the same class have similar risk-benefit ratios and therefore prescribe them irrespective of whether or not they are licensed for the respective indication. However, there is increasing evidence suggesting a relevant variation in the risk profile between individual antidepressants within one class. Furthermore, the risk of drug-drug interactions may vary between individual antidepressants. For example, the concomitant use of the TCAs clomipramine or imipramine with certain opioids can—similarly to SSRIs—lead to the partially life-threatening serotonin syndrome, while this is not the case for other TCAs such as amitriptyline, doxepine or trimipramine. In view of the high prevalence of opioid use among off-label users of antidepressants (19%), this potential interaction may require more attention among prescribing physicians.

The similarity between off- and on-label users regarding the summary measures of (co-)morbidity shown in Table 1 as well as regarding conditions that are contraindications of many antidepressants (eg, renal failure) suggests that off-label users of antidepressants are not healthier compared to on-label users and may thus carry a risk of adverse events at least similar to on-label users, if not worse. This also underlines the importance of conducting studies on the safety of off-label use among older adults, ideally for individual antidepressants in view of the aspect mentioned before.

The finding that there were also some prescriptions of reboxetine in our study population (ie, in patients above the age of 65), although reboxetine is contraindicated in patients of this age, is in line with prior findings showing that age restrictions are not always considered by prescribers. In clinical practice, the proportion of off-label use may even be higher according to our analyses. While we estimated the proportion of off-label use based on indications and age, the presence of contraindications represents another source of off-label use. The most frequent contraindications for antidepressant use are renal impairment, kidney diseases, cardiovascular diseases such as hypertension or arrhythmia, and the concomitant use of drugs metabolized via cytochrome P450 and its isoenzymes, drugs with anticholinergic properties or opioids. As expected and supported by our analyses, these contraindications are rather prevalent in the older population. It should be monitored whether these contraindications are adequately taken into account in clinical practice as regards, for example, the dosing or the overall judgement of the risk-benefit ratio. Regarding reboxetine, physicians should consider an alternative antidepressant that is indicated for the treatment of older adults.

4.4 | Strengths and weaknesses of the study

There are strengths and limitations to our study. One limitation might be that this analysis overestimates off-label use because the coding of depression could be incomplete or incorrect in claims data. Even though the health system expects physicians to code the disease(s) for which they treat their patients once per quarter, underreporting cannot be fully ruled out. To minimise this limitation, we also assigned persons with unspecific codes for mixed anxiety and depression (F41.2) and for adjustment disorders (F43.2) to the group of on-label users. This way, the estimate of overall off-label use was as conservative as possible. Excluding these two codes in the definition of depression would have increased overall off-label use by 5-6 percentage points. Furthermore, in the base-case analysis, we assigned indications of the original product also to generic products to provide a conservative estimate of off-label use. Underreporting might still occur when depression is only a concomitant disease, but the comparison between on- and off-label users showing similar prevalences of diseases such as cancer or COPD did not support this hypothesis.

We have chosen a period of 1 year before the first prescription to consider codes for depression. We are aware that this bears the risk of underestimating off-label use in view of patterns described by a Dutch study, suggesting that antidepressants are often used longer than needed. However, as our analysis primarily aimed to provide a conservative estimate of off-label use the look-back period of 1 year seems justified. The focus on outpatient diagnoses in our analysis seems justified given that the vast majority (>97%) of depression cases in Germany is treated in the outpatient setting only or in the inpatient and outpatient setting combined. We thus do not expect that the proportion of off-label users would have changed considerably if inpatient diagnoses had been considered additionally. We decided to use the most recent indications of the antidepressants rather than the indications at the time when the respective antidepressant was prescribed to avoid showing trends caused by label
changes. Given that changes in indications over time are mainly extensions this approach may underestimate off-label use in the earlier years of the study period.

A strength of our study is the database used allowing us to assess antidepressant use in a large and well-defined sample of older adults. Given the absence of recall and volunteer bias our study provides real-world evidence which is of high value in healthcare research. Due to the large sample size and comprehensive information available in claims data detailed analyses such as stratification by individual antidepressants and description of comorbidities were possible. Furthermore, we were able to assess if there were important time trends by comparing off-label use for all years between 2009 and 2015. However, there is no optimal database with which to address this research question. Our database, for example, does not include direct information on the prescribed dose, which would provide another opportunity to distinguish between on- and off-label use for some antidepressants. Nonetheless, it is reassuring that the overall proportion of off-label use in our study is consistent with a recent study from Germany assessing overtreatment based on primary data which minimizes the concern that claims data may lack relevant information on diagnoses.

4.5 | Unanswered questions and future research

From a public health perspective, an important next step would be to assess whether older adults using antidepressants off-label are actually at an increased risk of adverse drug reactions compared to on-label users. Available evidence on drug safety among off-label users vs on-label users is generally scarce and not focussed on antidepressants but it supports concerns that off-label use could be associated with a higher risk of undesired effects. Furthermore, studies among prescribing physicians to investigate further details and reasons for potential off-label use of antidepressants are needed. Intervention studies on how to improve knowledge and awareness of differences in indications and contraindications between individual antidepressants should also be key goals for future research.

5 | CONCLUSION

Our study suggests a high prevalence of off-label antidepressant use among older adults in Germany. Although there was variation, this high prevalence of off-label use was not restricted to certain classes of antidepressants or individual antidepressants. Given the uncertainties regarding the reasons for and risk-benefit ratios of this off-label use, studies at the prescriber level as well as studies investigating the safety of off-label use among older adults for individual antidepressants are urgently needed.

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All authors work at an independent, nonprofit research institute, the Leibniz Institute for Prevention Research and Epidemiology - BIPS. Unrelated to this study, BIPS occasionally conducts studies financed by the pharmaceutical industry. Almost exclusively, these are postauthorization safety studies requested by health authorities. The design and conduct of these studies as well as the interpretation and publication are not influenced by the pharmaceutical industry. The study presented was not funded by the pharmaceutical industry.

CONTRIBUTORS

W.S. conceptualised the research question. All authors contributed to the design of the study and the interpretation of the results. Data analysis was performed by W.S. (with double independent programming performed by F.G., who is mentioned in the acknowledgements) and T.R. supervised all statistical analyses. The manuscript was drafted by W.S. and critically revised by all other authors. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

As we are not the owners of the data we are not legally entitled to grant access to the data of the German Pharmacoepidemiological Research Database GePaRD. In accordance with German data protection regulations, access to the data is granted only to BIPS employees on the BIPS premises and in the context of approved research projects. Third parties may only access the data in cooperation with BIPS and after signing an agreement for guest researchers at BIPS.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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