Leibniz Institute for Prevention Research and Epidemiology – BIPS

Utilization of antidepressants in vulnerable groups of patients: investigations using data from the German Pharmacoepidemiological Research Database (GePaRD)

Kumulative Dissertation zur Erlangung der Doktorwürde

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Zusammenfassung

Antidepressiva gehören seit vielen Jahren zu den am häufigsten verschriebenen Arzneimitteln, und ihre Anwendung findet auch in vulnerablen Patientengruppen wie Ältere und Schwangere statt. Allerdings sind für diese Gruppen wenige Informationen zur Anwendung sowie zur Sicherheit der Anwendung verfügbar. Ursächlich hierfür ist mitunter, dass vulnerable Gruppen in klinischen Studien zur Sicherheit von Arzneimitteln aus verschiedenen Gründen oftmals unterrepräsentiert oder gar ausgeschlossen sind. Gleichzeitig sind dadurch die in den klinischen Studien gewonnenen Erkenntnisse nicht 1:1 auf die vulnerablen Patientengruppen übertragbar, da Unterschiede hinsichtlich Komorbiditäten, Komedikationen und Pharmakokinetik bestehen. Es werden daher weitere Studien unter Realbedingungen benötigt, um tatsächliche Anwendungsgebiete, Nutzergruppen und die Sicherheit zu beschreiben. Primärdatenbasierte Studien sind hier nicht immer möglich oder ausreichend.

Im Rahmen dieser Dissertation werden daher mittels der Daten der Pharmakoepidemiologischen Forschungsdatenbank GePaRD der Gebrauch und die Sicherheit von Antidepressiva bei Älteren und Schwangeren untersucht. Hierbei wird mittels einer eingebetteten Fall-Kontroll-Studie basierend auf einer Kohorte von Antidepressiva-Neunutzern das Risiko für Schlaganfälle durch Hirnblutung als potentielle Nebenwirkung geschätzt.

Basierend auf älteren Antidepressiva-Neunutzern wird zudem beschrieben, wie häufig Antidepressiva ohne das Vorliegen einer Indikation verschrieben werden. Weiterhin werden Schwangerschaften charakterisiert, in deren Verlauf Johanniskraut als Antidepressivum verschrieben wurde. Hierbei wird auch das relative Risiko von Fehlbildungen bei Kindern, deren Mütter im ersten Trimester Johanniskraut eingenommen haben, im Vergleich zu Kindern, deren Mütter im zweiten oder dritten Trimester Johanniskraut eingenommen haben, ermittelt.

Es wird dabei aufgezeigt, dass der Gebrauch von bestimmten Antidepressiva, die die Wiederaufnahme von Serotonin oder Noradrenalin hemmen, im Vergleich zu Antidepressiva ohne diese Eigenschaft bei älteren Menschen zu einem erhöhten Risiko für das Auftreten von Schlaganfällen durch Hirnblutung führt. Zudem werden Antidepressiva in dieser Personengruppe häufig außerhalb der zugelassenen Indikationen (off-label) verschrieben. Gleichzeitig bieten die Ergebnisse Anlass zur Vermutung, dass Ärzte die Indikationen verschiedener Antidepressiva nicht zwingend beachten. Diese Annahme beruht darauf, dass mit Schlafstörungen und Schmerzsyndromen zwei Grunderkrankungen als potentielle indizierende Erkrankungen erkannt wurden, die nur bei bestimmten Antidepressiva zugelassene Indikationen darstellen. Weiterhin zeigt sich, dass Johanniskraut als pflanzliches Antidepressivum trotz fehlender Informationen zur Sicher-

heit während der Schwangerschaft insbesondere während des ersten Trimesters angewendet wird. Hinweise bestehen auf ein (nicht signifikant) erhöhtes Risiko von Herzseptumdefekten bei Exposition im ersten Trimester im Vergleich zum zweiten oder dritten Trimester.

Die Ergebnisse verdeutlichen, dass Antidepressiva trotz unzureichender Informationen aus klinischen Studien zur Sicherheit durch Unterrepräsentation häufig in vulnerablen Patientengruppen angewendet werden. Dabei zeigt sich, dass aufgrund der Unterschiede zwischen verschiedenen Wirkstoffen hinsichtlich des Risikos für Schlaganfälle durch Hirnblutungen und der verschiedenen Indikationen stärker auf die einzelnen Risikoprofile der Wirkstoffe, aber auch auf die Patientencharakteristika bei der Verschreibung von Antidepressiva geachtet werden muss. Risiken und Nutzen des Gebrauchs sollten vorsichtig gegeneinander abgewogen werden bevor Antidepressiva verschrieben werden. Dabei sollten unnötige Risiken durch die Verwendung von Antidepressiva mit bekannt schlechterem Nebenwirkungsprofil oder durch eine Anwendung außerhalb der bestehenden Indikationen vermieden werden. Die Erkenntnisse zum Johanniskrautgebrauch zeigen, dass pflanzliche Alternativen zu konventionellen Antidepressiva durchaus Anwendung finden, auch wenn hiervon mangels Informationen zur Sicherheit von Arzneimittelbehörden abgeraten wird. Zudem zeigt sich mit dem (nicht signifikant) erhöhten relativen Risiko, dass eine

Einnahme von Johanniskraut nur nach strengster Risikoabwägung erfolgen sollte.

Für beide vulnerablen Gruppen ist abschließen festzuhalten, dass durch die Ärzte eine genaue Risiko-Nutzen-Abwägung bei der Anwendung von Antidepressiva erfolgen sollte. Dabei sollte weiterhin stärker auf die bekannten Risiken und bestehenden Indikationen geachtet sowie die Unterschiede zwischen verschiedenen Wirkstoffen innerhalb einer Wirkstoffgruppe geachtet werden. Für alle vorgestellten Anwendungsfälle sind weitere Studien angebracht, um die gewonnenen Erkenntnisse zu prüfen, weiter zu ergänzen oder auch zu untermauern.

Summary

Antidepressants have been among the most commonly prescribed medications for many years, and they are also used in vulnerable patient groups such as the elderly and pregnant women. However, little information is available on the use and safety of antidepressant use for these groups. One of the main reasons is that vulnerable groups are often underrepresented or even excluded from clinical trials on the safety of drugs, for various reasons. At the same time, the findings obtained in the clinical studies cannot be transferred 1:1 to the vulnerable patient groups due to differences in comorbidity, comedication and pharmacokinetics. Therefore, further studies under real-life conditions are needed to describe fields of application, user groups and safety of antidepressants under real-life conditions. Here, studies based on primary data collection are not always possible or sufficient.

Within this dissertation the use and safety of antidepressants in the elderly and pregnant women as two important groups of vulnerable patients will therefore be investigated, using data from the Pharmacoepidemiological Research Database GePaRD. Based on case-control study nested in a cohort of antidepressant users, the risk of stroke due to brain haemorrhage as a potential adverse event is estimated. Based on the cohort of older antidepressant initiators, the frequency of antidepressant prescrib-

ing at the absence of an indicating diagnosis, i.e. off-label use, is also described. Furthermore, pregnancies exposed to St. John's wort as an antidepressant are characterized. The relative risk of malformations in children whose mothers used St. John's wort during the first trimester compared to children whose mothers used St. John's wort in the second or third trimester is also determined.

Within these studies, it is shown that the use of certain antidepressants inhibiting the reuptake of serotonin or noradrenaline compared to other antidepressants without this mode of action leads to an increased risk of haemorrhagic stroke in the elderly compared with antidepressants without this property. In addition, antidepressants are frequently prescribed outside the approved indications (off-label) in this group of persons. At the same time, the results give reason to suspect that physicians do not necessarily observe the indications for various antidepressants. This can be assumed as sleep disorders and pain syndromes, which are approved indications for certain antidepressants only, were identified as potential indications in many patients. Furthermore, it appears that St. John's wort as an herbal antidepressant is used during pregnancy, especially during the first trimester, despite a lack of information on safety. The results hint at a (nonsignificant) increased risk of cardiac septal effects for babies ex-

posed in utero during the first trimester compared with the second or third trimester.

The results highlight that antidepressants are frequently used in vulnerable patient populations despite insufficient information from clinical trials on safety due to underrepresentation. Given the differences between different agents in terms of risk for stroke from cerebral haemorrhage and the different indications, the results show that more attention needs to be paid to the individual risk profiles of the agents, as well as to patient characteristics when prescribing antidepressants. Risks and benefits of use should be carefully weighed before prescribing antidepressants. It should be avoided to take unnecessary risks by using antidepressants with known worse side effect profiles or by using them outside of existing indications. The evidence on St. John's wort use shows that herbal alternatives to conventional antidepressants are indeed used, even if they are discouraged by drug authorities due to lack of information on safety. In addition, the (non-significantly) increased relative risk shows that St. John's wort should only be used after strict risk assessment.

For both vulnerable groups, it can be concluded that physicians should perform a careful risk-benefit assessment when prescribing antidepressants. Further, more attention should be warranted to the known risks and existing indications, as well as to the differences between various ac-

tive substances within a group of active substances when prescribing antidepressants to vulnerable groups of patients. For all cases of application presented, further studies are needed in order to further evaluate, support or also substantiate the findings obtained.

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List of abbreviations

ADR	Adverse drug reaction
ATC	Anatomical Therapeutic Chemical Classification System
AMG	Arzneimittelgesetz
BIPS	Leibniz Institute for Prevention Research and Epidemiology – BIPS
CI	Confidence nterval
CT	Computed tomography scan
CYP	Cytochrome p-450
DDD	Defined Daily Dosis
EMA	European Medicines Agency
EBM	Einheitlicher Bewertungsmaßstab
FDA	US Food and Drug Agency
GePaRD	German Pharmacoepidemiological Research Database
ICD-10-GM	International Classification of Diseases, 10th revision, German modification
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
MAO	Monoamine oxidase inhibitor
MRI	Magnetic resonance imaging
NARI	Noradrenaline reuptake inhibitor
NaSSA	Noradrenegic and specific serotonergic antidepressant
OLU	Off-label use
OPS	Operationen- und Prozedurenschlüssel
OR	Odds ratio
OTC	Over-the-counter drug

P	Publication
RCT	Randomized clinical trial
RR	Relative risk
SHI	Statutory health insurance provider
SMPC	Summary of product characteristics
SSNRI	Selective serotonin and noradrenaline reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tri- and tetracyclic antidepressant

1. Introduction

1.1. Background & current state of research

Over the past two decades, the use of antidepressants has increased worldwide (1). Current literature does not provide a conclusive picture whether this trends was also seen for depression (2, 3), but a recent study based on German claims data from the ambulatory setting covering the years 2009 to 2017 reports an increase of prevalence of depression (4). Thus, the rise in utilization can, at least to some extent, be explained for Germany by underlying disease trends.

When prescribing antidepressants to patients, physicians should evaluate the benefits and especially the potential harm that might be caused to the patient when using the drug. In general, the knowledge on potential harm caused by the utilization of a drug is derived from (randomized) clinical trials (RCTs). As clinical trials are often too short, based on too few and in terms of inclusion criteria too narrowly selected patients with a too low median age and conducted in an optimum setting, also studies in real-world settings are needed (5). This gave rise to the utilization of data collected in routine care to be used for drug utilization and safety research (6-8).

For antidepressants, it is known that their use may cause a variety of adverse drug reactions (ADRs), such as anticholinergic effects (tachycardia, urinary retention, anhidrosis, fever, constipation), cardiovascular diseases (arrhythmia, hypertension, prolongation or shortening of QT-time in echocardiography), fractures, gastrointestinal symptoms and diseases (nausea, vomiting and diarrhoea), sedation, sleeping disorders, the serotonin syndrome, or weight gain (9, 10).

The potential harm from ADR in antidepressant use might be increased by (a) interactions of the antidepressant with lifestyle factors and/or concomitant use of other drugs, (b) by disregarding patient characteristics that might influence the prescribed dosage of the antidepressant or the general use of the drug, such as age, comorbidities or pregnancy, or (c) by using the drug for other purposes than the licensed indications (i.e. off-label use [OLU]), where information on safety may be missing or incomplete (11-13).

Even though the aspects just described under a) to c) are expected to play a role in real-life settings, there is limited knowledge about these issues, especially for vulnerable groups of patients. It is difficult to obtain this information from primary data studies in real-life settings, as the specific vulnerable groups of patients are often hard to recruit for participation or exempt from participation for ethical reasons (14-19).

In the context of healthcare and medicine, vulnerability of a patient can be defined as being at risk or in a state of physical and/or emotional and/or cognitive harm, which makes the patient more susceptible to additional harm (14). Generally, vulnerable groups of patients can therefore be defined by different factors such as age (with children and older adults being vulnerable), general health status, socio-economic factors and migrant status, among others.

Among the adult population, older adults and pregnant women represent two vulnerable groups of patients which are often exempt from clinical trials. It is often considered unethical to conduct trials including pregnant women as the teratogenic potential of a drug may not be known and cannot always be derived from animal studies, which in conclusion puts the foetus at risk (20). For older adults, the main reasons are comorbidity and use of other drugs for the treatment of these comorbidities with the inherent risk of ADR due to drug-drug-interactions (15, 21). Additionally, the assessment of drug utilization, life-style factors and factors influencing the prescribing behaviour of physicians in primary data studies can be challenging and prone to information bias (22, 23).

Considering that drug utilization and safety affects more than one life during pregnancy, and given the demographic change with an aging population where unnecessary health risks due to unsafe medication should be

avoided, these groups of patients will be further investigated within this dissertation.

The following sections therefore describe how adults aged 65 years and older, and pregnant women are represented in clinical trials, followed by a description of the current state of knowledge on the safety of antidepressants in these vulnerable groups of patients.

1.1.1 Representation of vulnerable groups of patients in drug utilization and drug safety research

When studying drug safety in RCTs, inclusion of vulnerable patients defined by age or overall health status is often restricted. Specifically, vulnerable groups of patients such as older adults and pregnant women should only be included in trials if they personally benefit or if the research cannot be carried out in a non-vulnerable group (24). Hence, due to the underrepresentation in RCTs, insights on drug safety cannot be (fully) applied to these groups, and it is why researchers and others have urged for vulnerable groups to be considered more adequately in RCTs (14, 15, 25).

Besides potential restrictions, recruiting vulnerable groups for observational studies can be difficult, as they might be hard to recruit (16-19). In observational studies where data on drug utilization and drug safety is col-

lected by means of questionnaires or the brown-bag-method (participants are asked to show all medication they have at home when interviewed, which will then be reviewed by a pharmacist) (26, 27), bias might also occur as exposure is not or falsely remembered (27-29).

1.1.1.1 Older Adults

The inclusion and exclusion of older adults in clinical trials per se has been long studied and discussed. The exclusion of older adults from clinical trials, especially in the pre-authorisation phase, has often been justified with differences in patient characteristics. However, in 1993 (i.e. almost 30 years ago) a guideline for the inclusion of older adults in clinical trials despite the differences in characteristics was published by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (30). From this point forward, the principles of this guideline were implemented by authorities, such as the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). Further, pharmaceutical companies should have implemented and adhered to this guideline in the conduct of clinical trials pre-authorization (15).

Despite the need to include older adults into clinical trials to ensure drug utilization is safe also in this more and more growing population, they of-

ten still are exempt due to age-based cut-offs or diseases which are increasing in prevalence with age (17, 19, 31). Further, even if all boundaries were set aside or lowered, one difficulty still remains when wanting to include more older adults into trials, as van Marum points out: there often is a generally lower willingness or motivation in this population to participate in trials (15).

The non-inclusion of older adults into clinical trials for the investigation of drug safety subsequently leads to certain problems in everyday care. One major concern lies within the differences of pharmacokinetics in young- to middle-aged adults – who represent the majority of people included in clinical trials – compared to older adults (19, 32). In older adults, the metabolism is often slower and thus, the drug may also be metabolised at a lower rate (33, 34). This would call for an adaptation of medication by for example reducing the dosage given to prevent potential overdosing (34).

For other observational primary data studies, such as cohort studies, inclusion of older adults is more feasible than for clinical trials as the inclusion criteria are less restrictive. Further, recruiting can be directly targeted at this group of patients, enhancing the chance of participation (21, 32). Hence, observational studies on drug utilization and drug safety with primary data collection are conducted to gain real-world insights.

However, primary data studies may not always be the perfect choice in drug utilization and drug safety research, as assessment of drug exposure is prone to recall bias. This is of even more concern in older adults where polypharmacy is highly prevalent and where recall bias might additionally be influenced by loss of memory (28, 29, 34, 35).

Overall, under-representation, the aforementioned obstacles that may not be fully resolvable to ensure a more frequent inclusion of older adults in clinical trials, as well as the risk of recall-bias in combination with difficulties in recruiting older adults for observational primary data studies on drug utilization and drug safety are still prevailing. Aiming for a safe utilization of drugs in older adults, it is therefore necessary a) for physicians to be cautious when prescribing drugs where there is only little information on the safety in older adults, and b) to conduct studies on the safety of drugs when used by older adults using real-world data such as claims data.

1.1.1.2 Pregnant women

Pregnancy is a very vulnerable phase in life, as actions and decisions for the health and well-being do not only affect the mother, but may also have an impact on the health of the unborn baby. It is therefore crucial that women can be assured about the safety of drug treatment not only

for themselves during the different phases of the pregnancy, but also for the unborn baby (25).

For more than 20 years, an increase in the utilization of drugs, both prescription and over-the-counter (OTC), during pregnancy has been observed in many countries in Europe and the US (36). The studies by Lupatelli and colleagues (37) for Europe and Mitchell and colleagues (38) for the US univocally report the use of at least one drug excluding vitamins, mineral supplements and iron in more than 80% of pregnancies. This increase is assumed to be caused by a rising age of mothers during pregnancy which is associated with an increased risk for complications and/or a rising prevalence of chronic conditions such as asthma, depression, diabetes, hypertension or rheumatic diseases. Here, it is crucial for the mother's health that treatment is continued during pregnancy (36). However, the safety of drugs has only been established for a few drugs while at the same time, some drugs such as valproate and retinoid drugs have been identified as safety threats due to their teratogenicity (37-39).

Hence, the need for information on drug safety during pregnancy is by and large not met, and pregnant women are mostly excluded from clinical trials, while newly occurring pregnancy in the course of a trial is also an exclusion criterion (or women may only be included when using contraception) (14, 25, 40). An inclusion of pregnant women in clinical trials would

be crucial for three main reasons: 1) women may experience new medical conditions needing treatment during pregnancy – examples would be hypertension, diabetes or depression – or suffer from persistent diseases (that may exacerbate during pregnancy) that need to be continuously treated also during pregnancy, e.g. asthma and depression, and treatment should be safe and effective (40, 41); 2) pregnancy invokes changes in the female body that affect many organ systems, increasing the likelihood that also pharmacokinetics is different during pregnancy which potentially causes changes in drug effects (36, 40, 41); 3) establishing safety of drug use for the foetus (40).

As these factors have not (yet) lead to a widespread inclusion of pregnant women in clinical trials, other approaches and methods but primary data study have been and need to be further explored to gain knowledge on this subject, e.g. by using secondary data (6, 42-45).

1.1.2 Utilization and safety of antidepressants

1.1.2.1 Older adults

As stated above, it is necessary to conduct studies on the utilization and safety of antidepressants in older adults using both primary and secondary data, as older adults are often exempt from clinical trials. Still, older adults also need treatment for depression, anxiety and other disorders for which

antidepressants are indicated (46, 47). Due to the insufficient consideration of older adults in trials in combination with both age-related changes of the metabolism and an age-correlated increase of comorbidities to be treated with drugs (34, 35), there is uncertainty related to risk of adverse drug reactions when using antidepressants.

Studies have focussed on general characteristic of older adults using antidepressants (48, 49), the prescribing patterns (and inherently the dosage) (50-52) as well as on the adequacy of prescribing of antidepressants to older adults (53, 54). However, little is known so far on the use of antidepressants for indications other than those licensed, i.e. OLU in older adults. As there is no information on the safety of OLU in the general adult population from trials as well, OLU is also a safety concern.

There is an increasing pool of studies investigating the safety of antidepressant use in older adults, having established a firm knowledge base on the risk of ADR such as gastro-intestinal bleedings (55, 56) and fractures or falls (57-59) . However, there are also potential adverse events for which the results from different studies are inconclusive. Among these is the haemorrhagic stroke (58, 60-66), which is a very severe adverse reaction with a reported case-fatality of 30-50% within the first month after disease onset (67-69). Both incidence and fatality of haemorrhagic stroke in-

crease with age (68). Some of the inconclusiveness may be attributed to differences in methodology, as pointed out in a systematic review (70).

1.1.2.2 Pregnant women

Antidepressants are needed for the treatment of newly occurring depressive disorders and as maintenance therapy. Discontinuation of treatment of known (psychiatric) disorders with antidepressants is a threat to the mother's health, and thus in consequence also for the baby's health. However, due to the exclusion of pregnant women in trials as described above, the safety of antidepressant use during pregnancy has been largely understudied. Only within the last about 10 to 15 years and in light of the global rise of antidepressant use, the knowledge on the safety of antidepressant use during pregnancy has been broadened (71).

The major driving force for this has been the exploration of secondary data to study drug utilization and drug safety during pregnancy (6, 43, 72-76). Studies based on secondary data have played a large role in establishing knowledge on which drugs are used when during pregnancy, and the pregnancy outcomes after drug use during pregnancy (77-80). More and more evidence based on real-world data is showing that the utilization of selective serotonin reuptake inhibitors (SSRIs) during the first trimester (e.g. citalopram, paroxetine) leads to an increase in the risk of cardiac mal-

formations (71). However, by and large, the herbal antidepressant St. John's wort is not included in the investigations of the safety of antidepressant use during pregnancy (78, 79, 81, 82). At the same time, the utilization of herbal and alternative medicines is rising globally, especially in women (83). A recent multi-national study found that about 30% of pregnant women used herbal medicines during pregnancy (84), while previous studies had reported prevalence between 1% and 57% (85-87). Further, as they are plant-based, such medicines as St. John's wort are often deemed a safe alternative to conventional medicines, and in this case antidepressant specifically (85, 88, 89). Even though authorities like the EMA advise to not use St. John's wort due to the missing information (90), it is likely that St. John's wort is nonetheless used during pregnancy as it is sold over the counter in drug stores and pharmacies.

Investigating the use of St. John's wort based on secondary data is not possible in most databases, as St. John's wort is not a prescription drug in most countries. In Germany, on the other hand, St. John's wort is available as both prescription and OTC medicine in the same strength. This potentially enables studying the utilization and safety of St. John's wort using claims data.

1.2. Objectives and research questions

Given the above stated lack of inclusion of vulnerable groups of patients in clinical trials in combination with the general increase of antidepressant prescriptions and the potential risks associated with antidepressant use, it is of public health relevance (a) to assess how antidepressants are used in real-life settings in vulnerable groups of patients and (b) to identify possible risks using real-world data, notably for older adults and pregnant women.

Automated databases containing health related information such as claims or medical record databases can help overcome some of the limitations presented, as they are largely unselected with respect to (among others) age and sex, and include information from everyday healthcare including drug prescriptions or dispensations. Thus, they facilitate studying drug utilization and drug safety in vulnerable groups of patients such as older adults. Applying suitable algorithms even opens the opportunity to conduct drug utilization and drug safety studies in pregnant women. Hence, they are a helpful source of data in cases where inclusion into trials and also non-trial primary data studies may be ethically not possible or questionable for populations, e.g. pregnant women. One such database is the German Pharmacoepidemiological Research Database (GePaRD),

which holds claims information from four statutory health insurance providers (SHIs) in Germany and which has been used and explored for drug utilization and drug safety research.

Against this backgroud, this dissertation aims to provide further insights on antidepressant use in vulnerable groups of patients based on real-world data, focusing on older adults and pregnant women. Specifically, the following research questions will be answered using GePaRD data:

1. Do antidepressants increase the risk of stroke due to brain haemorrhage in older adults and is there a difference in risk between individual substances?
2. What is the proportion of off-label use of antidepressants in older adults and what are potential factors for off-label prescribing?
3. When is St. John's wort administered during pregnancy, how can pregnant women using St. John's wort be characterised and what are the outcomes of exposed pregnancies?

By answering these questions, the usability of GePaRD for specific aspects of drug utilization research will also be investigated further.

2. Definitions and methods

To answer the proposed research questions, three studies were conducted. Within this chapter, the underlying data, definitions and methods will be described.

2.1. The German Pharmacoepidemiological Research Database (GePaRD)

The three investigations included in this dissertation are all based on claims data as GePaRD data were always used. GePaRD is a claims database including data from four German SHIs. As three out of the four health insurances are operating nation-wide, GePaRD covers all geographic regions of Germany. As of 2021, GePaRD includes data from more than 25 million patients who have been insured with one of the SHIs since 2004 or later until 2019 latest. About 20% of the German population are represented in GePaRD (91, 92).

Besides core data including sociodemographic factors and insurance periods, GePaRD holds data on outpatient treatments (coded according to the "Einheitlicher Bewertungsmaßstab" [EBM, English: Uniform Assessment Standard]), in- and outpatient diagnoses (coded according to the International Classification of Diseases, 10th revision, German modification [ICD-10-GM]), operations and procedures (coded according to the "Opera-

tionen- und Prozedurenschlüssel" [OPS, English operations and procedures key]) and reimbursed outpatient drug dispensations (classified according the Anatomical Therapeutic Chemical Classification System [ATC]) (92).

As it is a legal obligation for people living in Germany to have health insurance and as SHIs are forced by law to contract any citizen of Germany who wishes to be insured at the respective SHI, GePaRD is unselected with respect to age, sex and certain other factors such as race and migrant status. Related to income status, GePaRD is relatively unselected, as people above a certain annual income threshold, self- and state-employed people may chose private health insurance (applies to income-threshold, self-employment and public servants). Thus, there might be an underrepresentation of higher incomes. Unemployed people or people on retirement (excluding those with private health insurance) are also included in GePaRD (92).

2.2. Exposure: Antidepressants

Antidepressants are medication used for the treatment of neuropsychiatric disorders, especially depression (93). The utilization of an antidepressant in the treatment of depression depends on the causes and symptoms of the disease, as well as on the severity and patient character-

istics (94, 95). Despite extensive research, the full mechanisms of why and how antidepressants work have not been fully identified yet (93, 96). Currently, it is known that there is an imbalance of neurotransmitters, especially of serotonin, in the synaptic gap. Further, an increase of levels of serotonin in the synaptic gap needs to be achieved for faster remission of depression (93, 96). However, an increase of serotonin-levels is already measurable a few hours after first application of an antidepressant, while improvement of mental health only manifests after several days to weeks. It has therefore been hypothesized that there are secondary and tertiary mechanisms following the increase of serotonin levels related to functional connectivity of different regions of the brain and to neuroplasticity (97, 98). Potentially, these mechanisms are activated or boosted by the higher levels of serotonin and cause the depression to improve (93).

Looking at the different antidepressants, there are two aspects that are primarily considered to classify antidepressants: (a) their chemical structure and/or (b) their pharmacological profile. Older classification systems focus on the chemical structure, while newer systems focus on the primary target point in the central nervous system of each respective antidepressant (96). Within this dissertation, antidepressants were classified in close relation to their primary target point in the central nervous system, as also suggested by e.g. Regen and Benkert (96): i) tricyclic antidepres-

sants (TCA; also called non-selective monoamine oxidase inhibitors), ii) selective serotonin reuptake inhibitors (SSRI), iii) monoamine oxidase inhibitors (MAO), iv) selective serotonin and noradrenaline reuptake inhibitors (SSNRI), v) noradrenergic and specific serotonergic antidepressants (NaSSA), vi) noradrenaline reuptake inhibitors (NARI), vii) herbal antidepressants, viii) antidepressants with other mechanisms (for the purpose of this dissertation referred to as other antidepressants). Appendix A. shows which active substances identified by their ATC-code have been considered for which category. Only active substances which had marketing authorisation in Germany between 2004 and 2017 are included in this list, as these are the substances available in Germany during the study periods of the investigations for this dissertation.

Within GePaRD, drugs can be identified via their ATC-code. For the purpose of this dissertation, all active substances identified by the ATC code "N06A" were considered as antidepressants. Exceptions from this are specified for each individual study, if necessary. As the prescribed daily dose and the dosage regimen are not included in GePaRD, duration of exposure has to be estimated. Using the defined daily dose (DDD) included in each package dispensed and the number of packages dispensed, duration of exposure is estimated by multiplying the DDDs per package with the respective amount of packages (92, 99).

For several antidepressants, their mode of action relates to changes of the levels of serotonin in the human body. Serotonin is also involved in haemostasis, which potentially interferes with other personal risk factors of antidepressant users. The following section therefore describes role of serotonin in haemostasis and potential related risks.

2.2.1. Serotonin and its role in haemostasis

Serotonin is an amine that is involved in several processes throughout the body (100). It is mainly produced in the gastro-intestinal structures of the human body and does not cross the blood-brain-barrier. Therefore, serotonin needed as a neurotransmitter in the central-nervous system is produced locally (101).

In the synaptic cleft, serotonin primarily acts as a neurotransmitter by activating the serotonergic receptors (93, 100). An imbalance of serotonin levels causing a dysfunction of neurotransmission is part of the pathogenesis of depression (100).

Besides its role as a neurotransmitter, serotonin is also involved in the blood clotting processes of the body (100, 102). To be transported in the blood, serotonin is taken up from plasma by thrombocytes and stored in the granules (100, 101). Once the process of coagulation is started (e.g. due to trauma), serotonin is released from the thrombocytes into the

blood. This causes an activation of serotonin receptors on the membrane of the platelets, which then promotes aggregation. While serotonin alone only has little effect, it enhances the effect of adenosine diphosphate, which is responsible for platelet activation (100, 102). Additionally, serotonin also promotes platelet aggregation where collagen is involved (100).

Some antidepressants, e.g. citalopram, fluoxetine, reboxetine and venlafaxine, inhibit the reuptake of serotonin (93, 100, 102): a) in the synaptic cleft by inhibition of carrier proteins at the presynaptic neuron causing serotonin to be available in the synaptic cleft for a longer time (93); b) generally in blood from plasma by thrombocytes causing lower serotonin levels in the platelets (100) and/or by hampering adhesion of platelets to collagen or fibrinogen (103). Based on this mechanism, it has been argued that the utilizations of drugs inhibiting the (re-)uptake of serotonin into the human body may cause bleeding events as there are only insufficient amounts of serotonin to enhance coagulation (100, 102, 103). In short: such antidepressants could, in theory, be a risk factor for bleeding events.

Studies have been conducted to investigate this theory of a potentially higher risk for bleeding events in the use of antidepressants inhibiting the reuptake of serotonin. While the evidence generated suggests univocally that the utilization of certain antidepressants, especially SSRIs such as

citalopram and fluoxetine, increases the risk of gastro-intestinal bleedings (55, 104-106), the evidence is not as clear for haemorrhagic stroke (70).

To add further insights on both classes of antidepressants as well as individual active substances with serotonergic properties and the potential risk of haemorrhagic stroke just described, the study for the first publication was conducted.

As previously described, the use of antidepressants in two sub-entities of vulnerable groups of patients is the focus of this dissertation: older adults and pregnant women. The following sections define these populations, the respective aspects of drug utilization and the outcomes.

2.3. Study population: older adults

In accordance with many studies (57, 58, 107), older adults have been defined as people aged 65 years or older for this dissertation. This cut-off is often used as this is in many cases the starting point of retirement and when pension benefits may be claimed. It is believed that the origin of such cut-offs and starting points lies in the German welfare system introduced by the former imperial chancellor Otto von Bismarck (108). In 1889, a law on social welfare related to disability and age initiated by Bismarck was introduced whereby workers received pension benefits from an age of 70 and onwards (109). In 1911, this law was extended to salaried em-

ployees who received pension benefits from an age of 65 and onwards (110).

For underlying cohorts of the two studies focusing on older adults, age was assessed at the date of a first dispensation of an antidepressant after at least one year without a dispensation of an antidepressant.

Two aspects regarding the general utilization as well as the safety of antidepressant use will be investigated in older adults and thus need to be defined: Haemorrhagic stroke and OLU.

2.3.1. Haemorrhagic stroke

A haemorrhagic stroke is a stroke due to rupture of vessels in the head, leading to allocation of blood in the head causing pressure onto the brain, as opposed to ischemic stroke which is caused by thrombosis in the brain or vessels leading towards the brain (67, 68).

Worldwide, about 10 to 30 % of all strokes are haemorrhagic strokes (69), with 10-12% of strokes in Germany being due to brain haemorrhage. As for the ischemic stroke, the overall risk of experiencing the event rises with increasing age, and also the risk factors as well as the symptoms are similar (67, 68, 111). A distinction from ischemic stroke as well as the identification of the affected area can only be made by applying imaging pro-

cedures such as magnetic resonance imaging (MRI) or computed tomography scan (CT) (111).

For haemorrhagic stroke, there are different sub-types depending on the location of the bleeding in the head: intracerebral bleedings – which is the main definition – and subarachnoid bleedings (68, 111, 112).

Intracerebral bleedings are caused by mainly by spontaneous ruptures of small vessels in the brain tissue leading to bleedings directly into the brain tissue (67, 113). The risk factors, besides age, are hypertension and arteriosclerotic changes of vessels due to hypertension, angiopathy or malformations of vessels, smoking and alcohol abuse, as well as use of anticoagulants (67). Depending on the size and location of the bleeding, prognosis for survival and disability differ, with 38% to 52% of cases dying within the first month after the event (67, 68).

Generally, subarachnoid haemorrhages are bleedings into the subarachnoid space, which is an area in the brain between the arachnoid tissue or membrane surrounding the brain, and the brain itself (114, 115). Most frequently (85%) these bleedings are caused by rupture of an aneurism (114-116). As opposed to intracerebral bleedings, CT- or MRI-scans may not show the haemorrhage, and an additional puncture of cerebrospinal fluid is therefore needed in diagnostics (114-116). The risk factors for subarachnoid haemorrhage are similar to the risk-factors of intracerebral

bleeding with age, smoking, hypertension and excessive alcohol consumption being the most frequent risk factors. Additionally, genetic predisposition for aneurism as well as low levels of progesterone in females are risk factors (114, 116). The case-fatality rate varies between 8% and 67% (114), while the WHO reports that about 45% of patients with subarachnoid haemorrhage die within the first 30 days, and there is a 4.5-fold increase in death within the first year following the event for patients surviving the first month (69).

Given the fact that age and hypertension, which is a condition frequently found in older adults, are risk factors for haemorrhagic stroke by themselves, reducing further potential risk factors in older adults should be of public health concern.

For the context of the first publication for this dissertation, haemorrhagic stroke was defined as intracerebral bleeding, subarachnoid bleeding, as in accordance with previous publications and guidelines (60, 61, 64, 69, 112-116). Further, as this can be differentiated based on ICD-10-GM codes, also non-traumatic intracranial bleedings were included into the definition.

2.3.2. Off-label use

The aim of the study of the second publication was to estimate the proportion of antidepressants used off-label.

Generally, OLU can be defined as the use of drugs outside the licensed indications (or in other words: at the absence of indicating diagnoses) or in groups of patients for whom the use of the drug is not licensed (117-120). Additionally, OLU may also be defined as the use of drugs at the presence of contra-indications (121). All factors are based on a) the clinical trials conducted to evaluate the safety of the drug prior to marketing authorization (119), and at times also on b) studies such as phase IV trials or post-authorisation safety studies investigating the safety of the drug in a real-world setting (32). For the purpose of this dissertation, OLU will be defined as the use of drugs, specifically antidepressants, at the absence of indicating diagnoses or if the drug is not licensed in the use of older adults generally or sub-groups of older adults.

In clinical practice, OLU is a necessity as there are diseases for which no specific treatment is available. Additionally, vulnerable groups of patients are often treated off-label due to their vast exemption from clinical trials and the resulting lack of authorisation of the drug for these populations (11, 118-120). In these populations, OLU requires additional caution as the drug has not been tested thoroughly or at all. Therefore, unknown or un-

expected adverse drug reactions might occur in OLU and further impair the patient's health (11, 119). For older adults, this is even more relevant as the number of co-treated comorbidities rises with age and thus the risk of ADRs due to drug-drug interactions (54).

When prescribing a drug off-label, physicians should also be aware of potential legal implications. In Germany, § 84 of the "Arzneimittelgesetz" (AMG, "drug law") describes that liability of the manufacturer in the event of death or harm due to a drug is only given if the drug is used appropriately (paragraph 2, sentence 1) or if harm has been caused by insufficient or wrong labelling or professional information (paragraph 2, sentence 2) (122). Further, the "Arzneimittelrichtlinie" explicitly describes that OLU is only allowed if i) experts of the Federal Joint Committee and the manufacturer acknowledged that based on current research OLU is recommended in the therapeutic field, ii) the Federal Joint Committee has included this recommendation into the "Arzneimittelrichtlinie", and iii) the manufacturer has approved the intended use and this is also documented in an appendix to the "Arzneimittelrichtlinie". The physician then has to explicitly inform the patient on the intended OLU, and is required to give notice about any ADR (paragraph 30) (123).

Due to the given uncertainties regarding the safety of OLU, physicians should always inform a patient that a treatment would be off-label with

given uncertainties on the safety. Additionally, they should obtain informed consent from the patient for OLU to rule out any legal consequences in case of acute or lasting harms from adverse events (123).

Despite the potential safety issues related to OLU, this is rarely studied in adults, let alone older adults, as compared to children and information on the magnitude of OLU there, patient characteristics and outcomes are scarce. This is due to OLU being easier to identify in children as many drugs are not licensed for paediatric use (124-126), while for adults the indications have to be investigated in most cases. With respect to claims data, this implies a challenge as the indication is not given on the prescription and thus included in prescription data for most databases. For some drugs, and among these also the antidepressants agomelatine and reboxetine, assessing OLU is also easy in older adults, as the use of these drugs is not licensed in older adults (127, 128).

Even though drug dispensation data in GePaRD also do not hold the indication, information on coded diseases as putative indications and dispensed medications can be linked on patient-level, also considering proximity in time between diagnosis and dispensation. Additionally, physicians in Germany should code at least once per quarter the reasons for treatment, which would also be the reasoning for prescribing a drug.

Considering these aspects, OLU was assessed in older adults newly using an antidepressant indicated for the treatment of depression. Restricting the analysis to use of antidepressants approved for the treatment of depression only was performed to create a more homogenous group with respect to potential confounding by indication. Accordingly, the TCA opipramol (ATC code N06AA05) as well as the antidepressant tryptophan (ATC code N06AX02) were not considered, as they are not licensed for the treatment of depression in Germany (96, 129, 130).

2.4. Study population: Pregnant women

2.4.1. Identifying pregnancies in GePaRD

It is rather easy to collect information on start, duration, end and type of pregnancy outcome in primary data studies as women and/or physicians can be directly asked about these parameters, and medical files of the respective woman could additionally be used (131). Identifying pregnancies from secondary data, however, is not as easy as certain information is fully missing or incomplete. Most importantly, there is no information on the last menstrual period, which marks the start-day of a pregnancy (42, 43, 74, 132-134).

Usually, the date of the last menstrual period is used to calculate the duration of a pregnancy. As this information, however, is not included in

GePaRD (and also other databases), algorithms need to be developed and applied to identify pregnancies and estimate their duration. Such algorithms are based on diagnosis codes, codes for treatment and procedures, potentially a date of delivery as well as knowledge on the mean duration of a pregnancy and the frequency of different outcomes (6, 42, 74).

For GePaRD, algorithms have been developed to estimate both the beginning and the ending of a pregnancy (43, 134). Additionally, there is an algorithm by which mothers and babies can be linked via direct and indirect linkage (135), enabling to study effects of drug exposure in-utero on babies. About 75% of mother-baby-pairs can be identified from direct linkage via a family identifier. Among these pairs, further information such as the hospital or outpatient delivery date is available for about 97% of pairs. For indirect linkage, this proportion is only slightly lower (96%) (135). To have the highest certainty that mothers and babies were correctly linked, an updated version of the direct linkage was applied for the investigation of the utilization of St. John's wort during pregnancy and the respective pregnancy outcomes.

Per pregnancy, the utilization of St. John's wort was assessed via outpatient dispensations.

2.4.2. St. John's wort as prescription medicine

Among all antidepressants there is also one herbal antidepressant: St. John's wort (ATC codes N06AH for homoeopathic preparations and N06AP for herbal medicines in the German adaptation of the ATC classification, see also Appendix A.). The effectiveness of St. John's wort in the treatment of depression has been shown in clinical trials, where St. John's wort has also shown a higher effectiveness compared to conventional antidepressants (136, 137). It is known that St. John's wort causes photosensitivity and may also cause adverse events due to drug-drug interactions as it is metabolized via CYP450 and p-glycoprotein (138-140).

Preparations of St. John's wort are available both over the counter (OTC, also in the form of food supplements) and as prescription medicine in Germany (141). Here, it can be chosen between different dosages of active compound in several different forms of applications, with the majority being tablets or capsules. These include dry extract of St. John's wort with ethanol, methanol or isopropanol as a solvent (drug-extract ratio: 2.5 – 8.1; see Appendix B. for examples that can potentially be identified in GePaRD (German only)). As prescription medicine, St. John's wort is licensed for the treatment of moderate depressive disorders as main indication (142), while mild depressive disorders are the main indication for

OTC preparations, and both can contain the same amount of active substance (143, 144).

However, there is no information on the effects St. John's wort may have on pregnancy and unborn babies, leading authorities to advise not to use St. John's wort during pregnancy (90).

With St. John's wort being available as prescription medicine reimbursed by SHIs, it is possible to investigate the utilization and safety of St. John's wort using GePaRD data by at the same time focusing on vulnerable groups of patients, in this case pregnant women.

2.5. Statistical methods

Different statistical methods were applied for the three original studies included in this dissertation. For all three original studies, characteristics were descriptively assessed by calculating percentages for categorical variables, while measures of location and dispersion were calculated for continuous variables.

For the risk of haemorrhagic stroke, matched and adjusted odds ratios (OR) with 95% CIs were estimated using conditional logistic regression. Comparisons were made for current, recent and past use of classes of antidepressants and TCA, as well as for current, recent and past use of individual antidepressants with amitriptyline (TCA) as comparator. Risk factors

for haemorrhagic stroke and certain medication that act as confounders were forced into the model. Other confounding variables were selected into the model using a backward selection process with Wald p-value ≤0.05 (145). Also, a full model was calculated as a sensitivity analysis.

OLU was assessed as proportions with 95% CIs using the Wilson score method (146). For the comparison of patients with OLU of antidepressants and on-label users, proportions were compared descriptively.

To roughly estimate the risk of malformations according to trimester of exposure to St. John's wort, relative risks with 95% CIs were calculated.

3. Results – Publications (P)

3.1. P 1: The risk of haemorrhagic stroke in antidepressant use: a nested case-control study

Drug Safety
https://doi.org/10.1007/s40264-019-00837-y

ORIGINAL RESEARCH ARTICLE

Check for updates

Antidepressants and the Risk of Hemorrhagic Stroke in the Elderly: a Nested Case–Control Study

Wiebke Schäfer[1] · Christina Princk[1] · Bianca Kollhorst[1] · Tania Schink[1]

For this publication (147), the risk of haemorrhagic stroke in older adults using antidepressants was estimated in a nested case-control study. Using GePaRD data from 2004 to 2015, a cohort of new users of antidepressants defined as patients who have not received a dispensation of an antidepressant for at least one year prior to the first dispensation found during the study period, aged 65 years or older was identified first. Within this cohort, cases of haemorrhagic stroke were identified from the first dispensation of an antidepressant onward by means of hospital discharge diagnosis. Up to 10 controls were then matched to each case based on sex, age (±1 year) and health insurance provider using risk-set sampling with time in cohort as time-axis. Exposure to antidepressants was assessed at the time of diagnosis (index day; for controls: the respective time-point of follow-up). To account for potential lower dosing and/or

medication errors, 150% of the DDDs of the last dispensation of an antidepressant was added to the days of supply assessed by the number of DDDs. Use of an antidepressant was then categorized as current use if the supply covered the index day or ended up to 30 days prior. In sensitivity analysis, 300% of the DDDs and no DDDs were added. The risk of haemorrhagic stroke was investigated for groups of antidepressants using TCA as reference as well as for individual substances using the TCA amitriptyline as reference. Stratified analyses were conducted a) according to the HAS-BLED score (148) to account for potential effect modification by general bleeding risk of individuals (two groups: low risk and moderate to high risk), and b) by prevalence of depression to account for potential confounding by indication or disease severity, as natural differences in serotonin levels due to severity of depression might influence the results.

The results showed that in 4,059 cases matched to 40,590 controls, there was an increased risk of haemorrhagic stroke in current use of SSRI (Odds Ratio [OR] 1.39, 95% confidence interval [CI] 1.22–1.58), SSNRI (1.69, 1.35-2.11), NaSSA (1.44, 1.22–1.69) and NARI (3.81, 1.54–9.43). The effects were robust across exposure definitions. Investigations in individual substances revealed that the risk differed within groups of antidepressants, as the risk for haemorrhagic stroke was only increased for citalopram (and escitalopram) in SSRIs, but not for sertraline and paroxetine.

Stratification according to the HAS-BLED score showed an increased risk in current use of SSRI, SSNRI, NaSSA and NARI in patients with a high baseline risk of overall bleeding. In patients with depression, the risk was increased in current users of SSRI, SSNRI, NaSSA and NARI, while the risk was only increased (but still less than for patients with depression) for current use of SSRI, SSNRI and NARI in patients without depression.

3.2. P 2: Estimating the proportion of off-label antidepressant use

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ORIGINAL ARTICLE

BJCP BRITISH PHARMACOLOGICAL SOCIETY

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

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Within this study (149), estimation of the proportion of OLU of new use of antidepressants in older adults was performed using GePaRD data for the years 2008 to 2015, using data from the year 2008 as baseline observation period for patients with a dispensation in 2009. Antidepressants were restricted to those preparations indicated in the treatment of depression. Therefore, new users of opipramol (ATC-code N06AA05) and tryptophan (ATC-code N06AX02) were not included into the cohort. Two different methods were used to assign indications to each preparation: a) the most recent indications of the original product were used (i.e. of the active compound, meaning that all generics and all formulations were considered as having the same indications); b) the most recent indications of each specific product according to the summary of product characteristics. Method a) considers current prescribing and dispensing practice where pharmacists are allowed to substitute the prescribed drug with another preparation containing the same active substance in the same dosage and

application form (aut-idem rule). Method b) takes into account that different dosages and/or application forms may be licensed for different indications, and producers of generic drugs are allowed to apply to have their generic licensed only for select indications of the original product.

OLU was defined as the absence of an outpatient coding for an indication given in the outpatient setting in the year before the first dispensation. In a sensitivity analysis, we also considered the full quarter of the dispensation and in the following quarter after the first dispensation. Additionally, we considered age restrictions for the use of agomelatine (ATC-code N06AX22) and reboxetine (ATC-code N06AX18) as the summaries of product characteristics had age 75 and older and age 65 and older, respectively, as a contra-indication during the study period. The proportion of OLU was estimated as the number of new users not having an indicating diagnosis (or age as contra-indication) within all new users of antidepressants. For annual proportions, the denominator was restricted to patients starting antidepressant use during the respective year.

Including all study years, 263,276 new users of the respective antidepressants were included. The proportion of OLU was 41% with only little variation between years. When applying method ii), the proportion of OLU was about 2 to 3 precentage points higher compared to method i). Generally, OLU was higher in men (49%; 95% CI 48–49%) compared to women (41%;

41–41%). Comparing groups of antidepressants, OLU was highest in new users of TCA (56%; 56–57%), followed by SSRI (42%; 42–42%). The proportion of OLU varied between active substances, also within groups of antidepressants. Among TCA, the highest proportion of OLU was found for trimipramine (TCA) with 66% of all prescriptions being off-label. Among all SSRI, the highest proportion of OLU was found for escitalopram (46%).

Characteristics of on- and off-label users only showed small differences. In off-label users, the most frequently coded comorbidities that could be an indication for prescribing an antidepressant off-label were insomnia (20%) and pain (72%).

3.3. P 3: Pregnancies exposed to St. John's wort and their outcomes

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Characterization of pregnancies exposed to St. John's wort and their outcomes: A claims data analysis

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The study population for this publication (150) consisted of all pregnancies in GePaRD ending between 2006 and 2016 having at least one dispensation of St. John's wort during pregnancy. Additionally, a continuous insurance period of at least one year before the beginning of the pregnancy was required to assess previous use of St. John's wort or other antidepressants as well as antiepileptic drugs to assess potential for drug-drug interactions. Further, coding of psychiatric comorbidities as potential indications for antidepressant use was evaluated during the year before the beginning of the pregnancy. For all pregnancies ending in live-birth, linkage of mothers and babies was performed using an established algorithm (135). In linked babies, coding of malformations was investigated and further verified by case-profile review and applying differentiation of major and minor malformations according to EUROCAT (151). Relative risks with 95% CIs were calculated for the occurrence of malformations in babies

exposed in utero during the first trimester compared to the second or third trimester.

Out of about 1.4 million pregnancies in GePaRD, 496 had a dispensation of St. John's wort during at least one trimester. Of these pregnancies, 78% were exposed during the first trimester only, while 15% were not exposed during the first trimester. About one third of all pregnancies had a dispensation of St. John's wort before the beginning of the pregnancy. General practitioners most frequently prescribed St. John's wort during the first trimester (70%), followed by psychiatrists and psychologists (20%). Characteristics of pregnant women such as age, education, comorbidity and comedication did not differentiate between pregnancies when stratifying by timing of exposure to St. John's wort. The median age was 32 years (29–36 years). Depression was coded before pregnancy for 68% of pregnant women, anxiety for 25% and both depression and anxiety were coded in 20% of pregnant women. Other antidepressants were used before the beginning of the pregnancy in 21% of pregnant women (during pregnancy: 12%), and there was a switch from using other antidepressants before the beginning of the pregnancy to St. John's wort during pregnancy in 9% of pregnant women included. Use of antiepileptic drugs was seen in 2% of pregnancies both before and during pregnancy.

About 10% of pregnancies ended during the first trimester. Non-live birth occurred in 11% of pregnancies with induced abortions as the most frequent reason for a premature end of pregnancy. Of all pregnancies ending in live-birth, 305 were linked to 312 children. In 47 of these children, coding of malformations was found. After further review, 18 babies were identified with major malformations. The relative risk for malformations for babies exposed in utero during the first trimester compared to the second or third trimester was 3.56 (0.48–26.17), with cardiac malformations being the most frequent malformation.

4. Discussion

The aim of this dissertation was to provide further insights into the utilization and safety of antidepressants in vulnerable groups of patients, namely older adults and pregnant women, using real-world data. Inherently, this dissertation wanted to further underline the usability of secondary data and the potentials that these data hold when vulnerable groups of patients are the population of interest. Within this chapter, the findings are first discussed individually based on the two vulnerable populations, followed by an overarching discussion.

4.1. Utilization of antidepressants in older adults

Regarding the utilization of antidepressants in older adults, the aim of this dissertation was to investigate if the utilization is associated with haemorrhagic stroke, and how often antidepressants are used off-label.

4.1.1. The risk of haemorrhagic stroke

Based on a cohort of approximately 600,000 older adults newly using antidepressants, the study on the risk of haemorrhagic stroke has found an increased risk in current use of SSRI, SSNRI and NARI compared to current use of TCA, with effects being driven by individual active substances within the groups of antidepressants. Based on active substance, the risk was highest for nortriptyline compared to amitriptyline as active comparator.

Effect modification was seen when stratifying the matched sets according to overall bleeding risk and depression diagnosis.

These results are in line with findings from the studies by Renoux et al. (64), where an increased risk for haemorrhagic stroke was also found for current use of SSRI compared to TCA in the overall adult population, as well as by Lee and colleagues (152), who found an increased risk of haemorrhagic stroke for SSNRI compared to SSRI. Furthermore, the results are supported by the meta-analysis by Douros and colleagues (70).

A comparison to the majority of other studies reporting effects for classes of antidepressants, however, is not possible due to methodological issues introducing bias. The inclusion of prevalent users (60, 65) potentially leads to bias due to depletion of susceptible patients and missing early outcome events (153-155). The occurrence of adverse events after initiation of a drug in relation to time has previously been classified into several subtypes (156) and can graphically be described by hazard functions (157, 158). According to the classification by Aronson and Ferner (156), haemorrhagic strokes would be expected to be intermediate reactions, as they are expected to occur after some delay, but not anymore after a certain time, and patients will discontinue treatment.

When wanting to study intermediate reactions, the study design has to be carefully considered to avoid bias from depletion of susceptibles due to

two principles. First, prevalent users did not experience adverse events or only tolerable side effects and are no longer or only at a very low rate susceptible to experiencing the ADR. At the same time and secondly, patients newly using a drug and experiencing other ADRs potentially stop treatment and select themselves out of the potential study population. Therefore, risk estimates reported in these studies are most likely underestimations of the true risk. This potential source of bias has been avoided in this dissertation by having nested the case-control sets into a cohort of incident users of antidepressants only (153-155).

For other studies, comparison of results was not possible as the studies did not consider time between initiation of the study drug and occurrence of haemorrhagic stroke correctly. By not considering time correctly, immortal-time-bias (for cohort studies) (159, 160) or time-window-bias (case-control studies) (154) was introduced causing misclassification of exposure time. In consequence, risk estimates were biased towards the null. For P1, this bias was avoided by performing risk-set-sampling using time in cohort as time axis for matching cases and controls. Controls therefore had been new users of antidepressants for the same amount of time as the cases they were matched to.

As analyses per individual antidepressant had only been performed by one other study and as the study did not distinguish between ischemic and

haemorrhagic stroke or use an active comparator (58), comparison and drawing final conclusions is hampered. Generally, the increase in risk observed for the respective individual antidepressants is plausible, as the inhibition of serotonin reuptake might cause too low levels of serotonin in the platelets which in consequence could hamper the activation process for haemostasis (100, 103). At the same time, the absence of a significant risk estimate does not mean that the respective antidepressant does not cause haemorrhagic stroke. Numbers of users of the respective antidepressants were potentially too low, leading to wider confidence intervals and/or sparse data (161). The finding that the risk is not consistent between antidepressants of the same class of antidepressants (e.g. between all SSRI) had not been shown by previous studies.

The analysis for individual antidepressants also further sheds light the degree of serotonin reuptake inhibition to potentially have an influence on the risk of haemorrhagic stroke. In the study by Renoux and colleagues (64), an increased risk was seen for strong inhibitors of serotonin. When sorting the results from the analysis by individual antidepressants presented in P1 (see Figure 1 below), the same effects cannot be seen as the risk of haemorrhagic stroke is not increased for most strong inhibitors, while it is for most antidepressant moderately inhibiting serotonin reuptake. Given the conflicting results, the influence of the degree of

reuptake inhibition on the risk of haemorrhagic stroke needs to be further investigated.

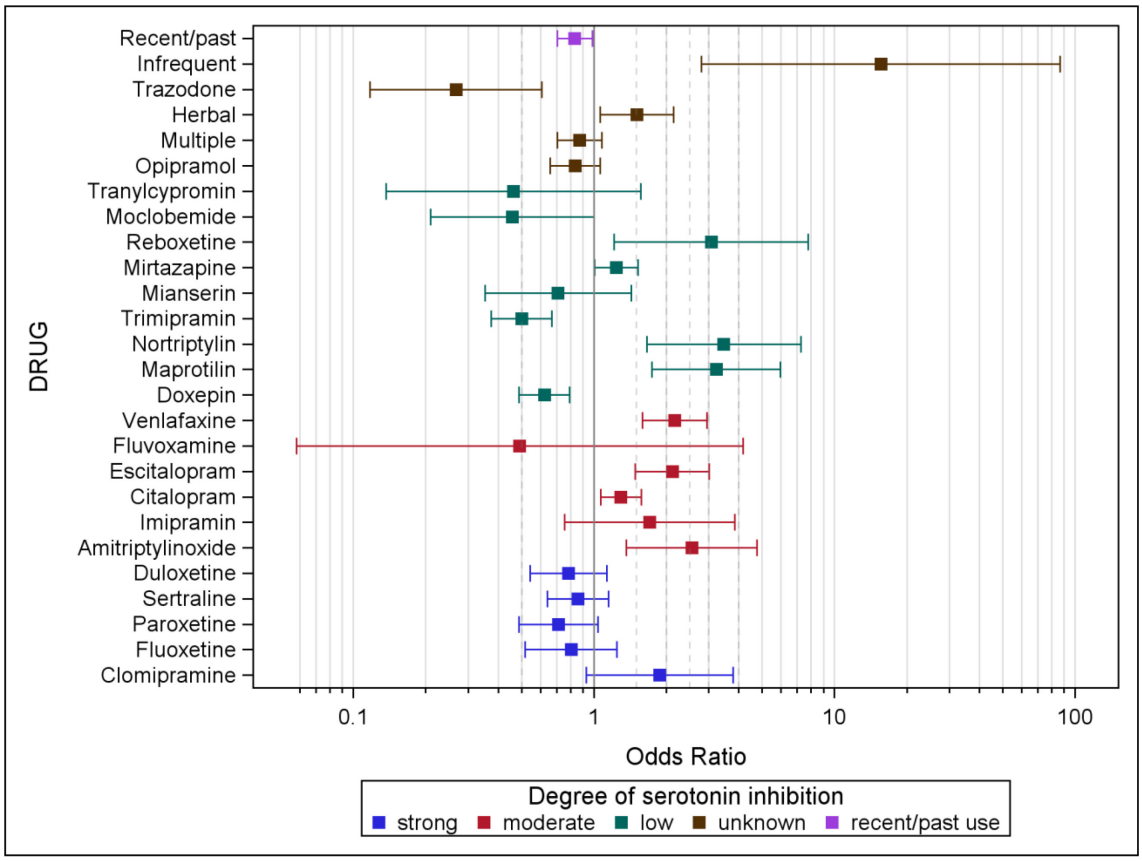

Figure 1. Risk of haemorrhagic stroke, by degree of serotonin reuptake inhibition

There are some limitations and difficulties underlying the findings of P1, especially with respect to the estimation of exposure. As only the last dispensation of an antidepressant prior to the event was considered, the estimation of exposure may have resulted in some misclassification. Estimating exposure prospectively and handling overlaps of dispensations / stockpiling as in a cohort approach could have resulted in a patient being currently exposed. Still, the chosen approach of exposure assessment at

time of event seems to be appropriate as the effects seen in the main analysis were robust when changing the estimation of supply to not adding any additional DDDs to the dispensed supply as well as upon adding 300% of the DDDs to the dispensed supply (as compared to 150% in the main analysis). This approach of adding additional supply to account for lower dosages or sinking adherence in older adults proposed by Gardasdottir et al. (50) is commonly used. However, there are other options for estimating exposure that also could have led to a different classification of exposure status at time of event. One of these options is the so-called waiting time distribution, which considers the time between first and following dispensation in each patient of a defined cohort defined by medication use. In recent years, this approach has been tested in a Danish database and further developed so that patient characteristics can be considered when estimating exposure using the waiting time distribution. This method has shown to provide different estimations according to factors such as age, which would be highly relevant in the cohort of older adults initiating antidepressant use presented within this dissertation (162-164).

Besides using a different method, the method chosen could also have been optimized for a more reliable estimation of exposure: a) Under the assumption that drugs are provided by the respective hospital during the stay, one would have to add the supply needed for the hospitalized time

to the length of supply of an outpatient dispensation; b) dose reductions are considered per active substance as specified in the SMPC for older adults. Given the differences between antidepressants where some require dose adjustments in older adults while others do not, and taking into account the differences also in half-life, it would be more accurate to adjust exposure assessment accordingly. However, this approach would not be feasible or only taking a lot of effort, as this information is not provided in secondary data and adding this information would be very time consuming.

The presented difficulties and different options in assessing exposure to antidepressants in older adults highlight one of the largest limitations when studying drug use in secondary data: in most databases including GePaRD, there is no information on the prescribed dosage. Sometimes, as in GePaRD, also the information on the use of most drugs during a hospital stay is not captured (165). Obtaining this information would be easier when using primary data defined as data obtained from e.g. interviews, (self-administered) surveys or case studies. Here, information could be obtained by means of questionnaires for patients and treating physicians, by consulting outpatient medical records and hospital charts, or by investigating medication possession using e.g. the brown-bag-method (also including OTC medication, which are potential confounding medication in

the study on haemorrhagic stroke) (26, 166). One limitation here is the risk of recall bias (which in older adults is even more important due to the potential onset of dementia) (27-29), which is not relevant in secondary data (5).

While such primary data studies on the risk of adverse events in antidepressant use have the advantage to facilitate assessment of dosage and actual use, there are also some disadvantages related to outcome ascertainment, capturing the study population and thus, study size. While it is rather easy to identify a cohort of more than 500,000 older adults newly using antidepressants based on secondary data as shown in P1, reaching such a large cohort within a short time-frame is near to impossible when doing primary data studies due to the financial and logistic expenses (8). Additionally, older adults are – as also mentioned in the introduction – hard to recruit (21, 32, 167). Further, including older adults of any socioeconomic status and additionally not having cultural or language barriers poses an additional challenge when performing studies based on primary data. Secondary data such as GePaRD are unselected in this regard due to being collected routinely for other purposes than research (167). However, this might also be a source of unmeasured confounding as the influence of these factors on drug prescription and use cannot or only partially be assessed and considered in analysis.

Secondary data are further needed, as the haemorrhagic stroke as an adverse event is a rather rare event, with low incidence and high case fatality and at the same time with rising prevalence with age (67, 68). Even within GePaRD as a large database with more than 25 million people, we only were able to identify approximately 4,000 cases from a cohort of more than 500,000 patients within a study period of 10 years. Primary data studies and even some smaller databases containing secondary data would not be able to capture the respective amount of events and achieve a sample size that would allow for meaningful statistical analysis of risk with good precision. An increase in risk as seen in P1 would potentially have been overlooked as the overall sample of patients with and without the outcome would have been too small (168). Even in the study presented based on GePaRD, the number of events was too small in some categories to allow analysis or risk estimates still had very broad confidence intervals due to small numbers. Still, numbers of cases and controls identified in GePaRD were large enough to facilitate the investigation if the risks previously found in other studies for classes of antidepressants were in fact class effects or if effects were caused by single substances within classes of antidepressants.

4.1.2. Off-label antidepressant use

It was aimed to answer the second research question of this dissertation within P2. Among more than 200,000 older adults newly using antidepressants indicated in the treatment of depression, about 41% did not have a coding of an indicating diagnosis, i.e. antidepressants were used off-label. This proportion was stable over time, with OLU being constantly higher in men (48%) compared to women (40%). The proportion of OLU varied between groups of antidepressants and also between substances of one group. On- and off-label users of antidepressants were similar in the majority of characteristics, with insomnia and pain as potential indicating diagnoses in off-label users.

Up to this point, only very few studies both based on either primary or secondary data had investigated the proportion of OLU in older adults using antidepressants (169-172). One study based on primary data from Germany showed very similar results with 42% of all antidepressants being prescribed off-label to older adults (169). Hanlon and colleagues (170) investigated overuse defined as the dispensation of an antidepressant at the absence of depression as an indication – which partly defines OLU – in residents of a veteran's nursing home and also found that about 42% older adults newly using antidepressants did not have an indicating diagnosis. Results based on a Canadian prescribing system showed a lower propor-

tion of OLU (24%), but comparability to this study is hampered as it is based on adults aged 18 years and older with a dispensation of an antidepressant (172), while the study population for P2 consisted only of adults aged 65 years and older with a dispensation of an antidepressant. The study by Wong and colleagues will therefore not be considered further for comparison.

A study by Thunander et al. (171) considering people aged 18 years and older in Sweden investigated over- and underuse of antidepressants. In their study cohort, however, overuse – which was defined in accordance with the definition by Hanlon et al. (170) – was very low in older adults with 4% of males and 11% of females using antidepressants off-label. Contrary to P2, OLU was higher in women compared to men. As this was self-reported diagnosis and drug use, the results have to be interpreted with caution.

Given the differences in indications, it is meaningful to assess OLU both in classes of antidepressants and – considering the heterogeneity of indications in some classes – also in individual antidepressants. In this respect, the results of P2 can only partly be compared to Hanlon and colleagues (170). By class of antidepressant, overuse was higher for both TCAs and SSRIs compared to our study. However, comparison is hampered as utilization of TCAs was only infrequent in the nursing home residents. The

studies by Boehlen and colleagues as well as Thunander and colleagues did not report results for classes of antidepressants or individual antidepressants (169, 171).

Insomnia and pain were the most frequent comorbidities in off-label users. Both are indications in some antidepressants such as the TCA clomipramine and imipramine which are indicated in the long-term treatment of pain (9, 173, 174), or the TCA trimipramine which is indicated for the treatment of depression with insomnia as a prevailing symptom (9, 175). This finding suggests that physicians might not consider the indications of a specific active substance thoroughly. The results rather hint that within a class of antidepressant – e.g. TCA – all individual active substances are assumed to be having the same risk-benefit profile. The findings from P1 and also other studies, however, show that this potentially is a misconception as risks for different adverse events vary within classes of antidepressants (58, 147, 176).

Further, the risk for adverse events due to a drug-drug-interaction of an off-label prescribed antidepressant with another drug differs as the potential for interaction is not the same for all active substances within one class of antidepressant (177). Revisiting the TCA, it has to be noted that clomipramine and imipramine hold a high potential for severe drug-drug-interaction with opioids – which are a rather frequent co-medication in

the study cohort with 19% of off-label users using opioids. Co-administration of opioids with the two TCA can lead to the life-threatening serotonin syndrome, while it is safe to use trimipramine concomitantly with opioids (178, 179). As the risk of drug-drug interactions rises with the number of different drugs used – which is often the case in older multi-morbid adults (54, 180-182) – the findings from P2 suggest that physicians should consider the indications (and contra-indications) more thoroughly when prescribing antidepressants to older adults.

The scarcity of other studies investigating OLU highlight two aspects: a) OLU is hard to capture in both primary and secondary data collection, and b) awareness for potential safety threats when administering antidepressants off-label seems to be low and needs to be improved. This is especially relevant in vulnerable groups of patients where there is already a gap in knowledge of safety when using the drugs for licensed indications due to under– or non-representation of these patients in clinical trials. Two studies have already investigated the potential risks associated with OLU, however this was not restricted to antidepressants, let alone older adults (12, 183). Therefore, P2 presents a step to close a gap in research and may help improve safe drug utilization in older adults.

The original study on OLU for this dissertation has some limitations and strengths. For the assessment of OLU, only outpatient diagnoses were

considered. It is therefore possible that OLU was overestimated by not considering inpatient diagnoses and therefore missing indications. However, physicians in Germany should code once per quarter the respective diagnoses for which treatment was sought according to coding guidelines (184). Therefore, outpatient prescriptions and dispensations should always be preceded by a respective indicating diagnosis. As we considered the full year before the dispensation and for sensitivity analyses also the following quarter for the identification of potentially indicating diagnoses (which did not substantially change the results), the possibility of having missed an earlier or later diagnosis as an indication is not relevant and the results seem to be reliable. This is further supported by the finding from Boehlen and colleagues based on primary data, where the proportion of OLU was very similar despite using primary data (169). Focusing on outpatient diagnoses only is also supported by an investigation of the treatment setting of patients with depression, where more than 97% of all patients with a diagnosis of depression were treated in the outpatient setting only or in both the in- and outpatient setting (185). Considering also inpatient diagnoses therefore would not have changed the results substantially.

A second limitation is directly linked to the first limitation: prescriptions in Germany do not hold any information on the diagnosis for which the physician prescribed the antidepressant. This may have also caused overesti-

mation of OLU, as potential indicating diagnoses may have been missed. Further, as the ICD-10-GM codes for the indicating diagnoses are not included in the pharmaceutical reference database for GePaRD and therefore had to be identified and added manually, it is possible that codes were missing and indicating diagnoses therefore could not be matched.

A major strength of the study lies in the utilization of GePaRD data. In using GePaRD, the utilization of antidepressants was studied based on data stemming from everyday healthcare service provision for a large and well-defined sample of older adults, while recall and volunteer bias were not of concern.

Another advantage of analyses conducted for P2 is that OLU not was not only assessed based on the indications of the active substance according to the ATC-code, but also based on the indications of individual preparations considering all outpatient diagnoses and prescriptions on patient level. Even though indications are given for an active substance, manufacturers may not seek license for all indications for an individual preparations or as part of the indications of the name-brand drug might still be protected by patent (186). Differences can be seen between brand-name and generic drugs, as well as based on amount of active substance included and dosage form. Finally, it was possible to investigate if there were

larger trends over time as it was possible to assess OLU for all years between 2009 and 2015 individually.

4.2. Utilization of St. John's wort in pregnant women

Within P3, answers to the third research question of this dissertation were found. More than 75% of pregnancies with a dispensation of St. John's wort were exposed during the first trimester only, and 11% of pregnancies ended in non-live birth. In about one quarter of pregnancies, a diagnosis of depression or anxiety was found before the beginning of the pregnancy. In about 2% of pregnancies, there was concomitant use of potentially interacting antiepileptic drugs. In 18 out of 312 linked babies major malformations were found, with atrial septal defects as the most frequent malformation. Comparing babies exposed to St. John's wort in utero during the first trimester to those exposed during the second or third trimester, an elevated risk was found, but this was statistically not significant 3.56 (0.48–26.17).

Putting P3 into a larger perspective is difficult as no other study based on secondary data has yet investigated the utilization of St. John's wort during pregnancy – though investigations would potentially be possible, e.g. in the Dutch PHARMO database as St. John's wort was a registered medicine in the Netherlands in the past (187).

There are only two studies based on primary data to which these findings can be compared (188, 189). Except for age, which was similar in all three studies with a mean age of mothers of about 32 years, and duration of pregnancy, which was shorter in the original study presented here compared to both studies, characteristics of exposed pregnancies were similar to the study by Moretti and colleagues only (189). In both studies, exposure to St. John's wort was most frequent during the first trimester, and depression and/or anxiety as potential indications were also coded for the majority of women (189). Comparing the results to the study by Kolding and colleagues (188) revealed a higher prevalence of depression among exposed pregnancies, while comparison of timing of exposure is not possible as the study by Kolding et al. only reported exposure as before 17 weeks of gestation (188). Incomplete pregnancies were more frequent in the study by Moretti and colleagues (20% vs. 11%) (189), while they were less frequent in the study by Kolding and colleagues (3% vs. 11%) (188). These differences may be due to the methods by which both live and non-live births were identified in either study. The study design applied by Moretti and colleagues where pregnant women were included at about 11 weeks of gestation with a follow-up after the expected delivery date enables a rather complete assessment of pregnancy outcomes (189). Contrary, the study design chosen by Kolding and colleagues, which included only

women who at their first visit to the general physician during pregnancy wanted to carry the pregnancy to full term (i.e. those who indicated to plan an abortion were not included), potentially underestimated the rate of incomplete pregnancies (188). The algorithm to identify pregnancy outcomes in GePaRD generally also underestimates the number of incomplete pregnancies, as especially early spontaneous abortions cannot be captured due to coding. However, the observed frequency of incomplete pregnancies among pregnancies exposed to St. John's wort is almost twice as high as in the overall GePaRD population (11% vs. 6%) (43), therefore raising concerns about a causal relationship between utilization of St. John's wort during early pregnancy and incomplete pregnancies.

In the studies by Kolding and colleagues as well as Moretti and colleagues, the types of malformation found were malformations of the heart, of the urinary tract (specifically hypospadias) and musculoskeletal malformations (188, 189). The types of malformations found and reported in P3 are thus similar by anatomical location to those reported by the other studies. However, no case of hypospadias was found in GePaRD, which is potentially a chance finding. Also, musculoskeletal malformations could not be identified as they are coded far too frequently and unspecific in GePaRD to be meaningfully analysed (150). The case of microcephalus is a unique and unexpected finding in the results based on GePaRD, as microcephalus

is a very rare malformation with a prevalence of about 1 per 10,000 births in 2018 according to EUROCAT data (151).

Though the associations were not statistically significant, the malformations found in all three studies, especially malformations of the heart are plausible and generate the need to further investigate the hypothesis that the use of St. John's wort during pregnancy increases the risk for cardiac malformations. The findings are plausible as it has been shown in other studies that the use of antidepressants inhibiting the re-uptake of serotonin or serotonin and noradrenaline – a property that also St. John's wort is assumed to hold (96, 190, 191) – during pregnancy increases the risk for septal defects, especially atrial septal defects. At the same time, serotonin as a signalling molecule is needed in several mechanisms of foetal development such as the genesis of the heart (77, 79, 81, 192, 193). Therefore, it would not be unreasonable to assume that also the use of St. John's wort during pregnancy leads to an increased risk for cardiac malformations.

There are some limitations and strengths to this study, of which those not related to generally identifying pregnancies and malformations in babies using GePaRD will be presented in the following paragraph. Limitations and strengths regarding the identification of pregnancies and malformations in babies in general will be discussed in section 4.3.

The first limitation is that St. John's wort is a drug frequently sold OTC. Considering this factor, the pregnancies identified in GePaRD may not be representative of all pregnancies exposed to St. John's wort. They rather represent a specific sub-sample of pregnant women seeking health-care for their mental well-being and wanting to cautiously apply medication and nutritional supplements after consultation with their physician only. A potentially larger group of pregnant women will use St. John's wort without prior consultation as it can be found not only as OTC medication in pharmacies, but also among other nutritional supplements in drugstores which might (falsely) signal safety. Additionally, herbal medicines are often deemed or promoted as "natural" and therefore safe (89, 194). Further, the need or reasons for wanting to use St. John's wort are potentially different in women buying OTC preparations, with rather mild or only temporary symptoms needing to be eased. There might also be socio-demographic differences between pregnant women using St. John's wort as a prescription drug and those using OTC, but this would need to be investigated in a different study based on interviews.

As a further limitation it has to be noted that it is possible that pregnancies with a dispensation during only one trimester were in fact exposed for a longer time as fills of the drug were purchased OTC. Additionally, exposure was only estimated roughly per date of dispensation as the primary

aim of the study was to generally assess and describe patterns of utilization of St. John's wort during pregnancy. Misclassification of exposure therefore can have occurred, which also could be of more relevance if a dispensation occurred shortly before the beginning of the pregnancy and supply lasted during the first trimester. Such pregnancies would not have been identified and included by the study design selected, while they might be of special interest when investigating the occurrence of malformations. For a study on the risk of malformations in pregnancies exposed to St. John's wort it would therefore be necessary to further refine the definition of exposure also taking into consideration the dosage and amount of units dispensed.

Another limitation is the sample size when considering the relative risk of malformations. Even though it was about five-times higher than in primary data studies on the utilization of St. John's wort during pregnancy, the sample drawn from GePaRD is still too small, especially the size of the comparator group. This leads to statistical uncertainty and inaccuracy of the estimation of relative risk of malformations which is reflected in the broad confidence interval.

There are also several strengths to the study. As all information on all healthcare services, diagnoses and drug dispensations reimbursed by the statutory health insurances is included in GePaRD, it was possible to iden-

tify a comparably large number of pregnancies exposed to St. John's wort and to assess if there were changes in prescribing St. John's wort during pregnancy in the time-span from 2006 to 2016. Moreover, the information included in GePaRD facilitated investigating the concomitant use of antiepileptic drugs during pregnancy. This is of special concern as antiepileptic drugs are potentially interacting drugs by inhibiting the same CYP isoenzymes that St. John's wort induces. The effectiveness of antiepileptic drugs might be reduced with concomitant use as the induction of CYP isoenzymes by St. John's wort leads to the antiepileptic drug being metabolized too fast to come to full effect.

Using controls that were also exposed to St. John's wort, but not in the time window of the pregnancy that is critical for the genesis of malformations is another strength of this study. It is expected that selecting the controls from the same overall cohort minimizes differences between groups with respect to confounders, as described also for the principle of choosing a negative control for intrauterine exposure and causal effects (195). Despite the small sample size and low precision, the results from this comparison are important information for further investigations on this topic, whether it may be meta-analysis, animal in-vivo studies or primary or secondary data studies comparing pregnancies exposed to St.

John's wort e.g. to other antidepressants. They further can also be used for decision making for drug therapy in pregnancy.

As compared to other claims databases, the precise information on the beginning of the pregnancy as included in GePaRD leads to another advantage of P3 as opposed to other studies. Due to the given granularity, ascertainment of exposure during the first trimester, which is the most relevant trimester for the genesis of drug-induced malformations, can be seen as very accurate (134). This accuracy is an important stabilizing factor for the potential risk of malformations seen following first trimester exposure to St. John's wort. Misclassification of exposure is therefore not very likely.

Finally, another advantage derives from the possibility of linking mothers and babies in GePaRD, and the possibility to follow-up linked babies independently of their mother's records beyond birth. Due to this linkage, the investigation of malformations that were not diagnosed immediately at birth was enabled leading to more reliable estimates on the frequency of malformations.

4.3. Discussion of overall findings

The aim of this dissertation was to investigate the utilization of antidepressants in vulnerable groups of patients where evidence on drug utiliza-

tion and drug safety is scarce due to exemption from or underrepresentation in clinical trials. Pregnant women are often exempt from clinical trials due to ethical considerations and older adults due to comorbidity and comedication, despite depression being a highly prevalent disease in these sub-groups of adults and despite differences in pharmacokinetics in these populations. Hence, the focus of this dissertation was set to these populations.

Within P1 to P3, real-world evidence on the utilization and safety of antidepressants in vulnerable groups of patients was gained based on German claims data. Both older adults and pregnant women can be identified as large and rather unselected cohorts. From these cohorts, it can be seen that antidepressants are used frequently in these populations despite limited knowledge on the safety of antidepressant use in these groups. Furthermore, it was shown that unnecessary risks are taken as antidepressants are used outside licensed indications, used concomitantly with potentially interacting drugs and in the presence of risk factors for adverse events. Within P1, it has further been shown that large databases are needed to identify an increase in risk for generally seldom to rare events such as stroke due to brain haemorrhage, where primary data studies are often too small to detect events or underpowered to quantify risks.

Considering publications 1 and 2, it has been shown that a variety of antidepressants are used in older adults, irrespective on the current state of research and knowledge which substances are safest to prescribe to older adults. When comparing the types of antidepressants used in German older adults to other countries, both studies show that in Germany, many older adults still receive TCA as first choice of antidepressants, while SSRI are the most frequently used class of antidepressant in most other European (196) or western countries (49). This finding of high prescription rates of TCA in older adults is somewhat worrisome. It is known that TCA hold a higher risk of adverse events due to their anticholinergic properties, with many individual substances being classified as potentially inappropriate medication in older adults (53, 54, 197). The results further show that recommendations from treatment guidelines to not use TCA due to their unfavourable risk-profile for adverse events (94) seem not to be fully enforced in everyday care in Germany.

Both P1 and P3 further saw the concomitant utilization of different antidepressants in the respective vulnerable groups of patients. This is of particular concern as this might increase the risk for drug-drug interactions, e.g. specific TCA and SSRI should not be combined, as well as MAO with specific TCA and SSRI, and St. John's wort with specific TCA and SSRI (177). In both original studies, a non-negligible proportion of the study popula-

tion used several antidepressants concomitantly (P1: 12%, P3: 12% [and 68% having a diagnosis for depression which should be treated throughout pregnancy]). This high proportion of concomitant use of different antidepressants is roughly in line with the findings from other studies where 16% of older adults (198), and 12% of pregnant women (199) used two or more antidepressants at the same time. From many studies, the proportion of concomitant use of antidepressants can be assumed, but it is not clearly stated (58, 64, 66, 79, 82). In some cases, concomitant users were not included into the study cohorts, as for P2 (62, 78).

Within P1 and P2, it was found that more than 20 different individual antidepressants were used in older adults, and for many antidepressants the number of users allowed investigations and risks for individual substances. In other risk studies, individual antidepressants are rarely investigated (58), and also studies investigating the frequency of off-label use (which also might pose a risk for ADR) do not always focus on individual antidepressants (169, 171). Only the study by Wong and colleagues, which also made use of secondary data of drug prescriptions, investigated off-label use in different individual antidepressants (172), while Hanlon and colleagues only investigated the problems arising from the use of potentially inappropriate antidepressive medications in patients with depression, i.e. in most likely older on-label users of antidepressants (170). Given the het-

erogeneity of indications, modes of action as well as risk for ADR between individual antidepressants of one class, it seems more straightforward and correct to report results for individual substances. The lack of these results in combination with differences in methodology (58) or populations (172) make a comparison of P1 and P2 to other studies difficult. P1 and P2 therefore can be seen as an important asset in closing gaps of knowledge on the utilization and safety of individual antidepressants, also for comparatively infrequently used antidepressants. This level of detail has also been used in other safety studies focusing on adverse events in older antidepressant users, e.g. recently in two investigations on the risk of traumatic brain injuries as well as fractures (57, 176).

Finally, within all three publications it was shown that St. John's wort is used in both groups as an alternative to conventional antidepressants. Despite capturing only a potentially smaller proportion of all utilization of St. John's wort in claims data, the findings highlight that St. John's wort should not be excluded when studying the utilization and safety of antidepressants, if possible. In light of the high potential for drug-drug-interactions that St. John's wort holds as a potent inducer of CYP2C9 and CYP2C19 as well as the already well-known adverse event of photosensitivity of the skin (136, 142, 200), all options of gaining more information on the utilization and safety of this drug should be considered. This is es-

pecially relevant as plant-based treatment alternatives to conventional drugs gain more and more popularity. As previously described, it is often not possible to study the utilization and safety of St. John's wort using secondary data such as claims or electronic medical records due to St. John's wort being sold and dispensed primarily over the counter. Hence, primary data studies are needed to further investigate the utilization and safety of St. John's wort, leading back to one of the initial problems of capturing older adults and pregnant women in trials as well as other studies based on primary data. Primary data studies therefore should use targeted approaches to identify the utilization of St. John's wort and to appropriately include older adults or pregnant women. Linkage of claims data with data from primary data collection might be considered to overcome these problems.

In Germany, this could potentially be done for a subset of patients included in GePaRD if they are participants of the NAKO Gesundheitsstudie and consented in linkage of their data to GePaRD. For the NAKO Gesundheitsstudie, oversampling of older adults was performed to overcome the problems of underrepresentation (201, 202). As participants were further asked to bring all medication used within the past seven days to their interview and as these medication were systematically registered (201), the

data from the NAKO Gesundheitsstudie might also help to identify users of St. John's wort.

There are some strengths or advantages as well as limitations or disadvantages when investigating the utilization and safety of antidepressants in vulnerable groups of patients based on claims data.

One limitation is that there is no information included in GePaRD (or in secondary data generally, to be more precise) if a person really used the drug, i.e. misclassification of exposure and exposed time may have occurred. This is especially crucial for the presented safety study in older adults (P1) as well as for the investigation on the occurrence of malformations after exposure in-utero (P3), as a person may have falsely been classified as using the drug, while in reality only the prescription was filled and the antidepressant was not used or only briefly and then stopped (203). Early discontinuation may be attributed to early adverse drug reactions in antidepressant use such as headaches, gastro-intestinal effects, insomnia, dizziness and falls (204, 205). In older adults, there may further be adverse events from polypharmacy and related drug-drug interactions (96). For both studies, this might have caused bias away from the null as outcome cases were counted as under exposure, while they should have been counted in the control group. But as these early adverse events can also be tolerable to achieve the desired effect and as the increase in risk

was seen for different antidepressants with varying likelihood for early adverse events, early discontinuation potentially did not have a large influence on the overall results.

Compared to other sources of secondary data such as electronic medical records where there is only information that the drug was prescribed (5, 206), having the information that the antidepressant was indeed dispensed to the patient is an advantage as filling the prescription is a step towards the intent of using treatment. To be rather sure that a person indeed used the antidepressant, further investigations on the dispensations would be needed and considered in analyses. This would encompass investigating repeat dispensations, the amount of units and DDDs dispensed as well as the time passing between two dispensations. As dosage schemes are currently not available in dispensation data – changes to prescription form and prescribing practice where physicians have to provide either the dosage on the form or indicate that a medication plan was handed to the patient has only been introduced in 2020 (207), leading to this information only being available in future data years to be included in GePaRD – precision when assessing exposure is further hampered as it has to be estimated. P1 shows one example of estimating exposure at the day of the outcome by considering the date of the last dispensation of an antidepressant before the outcome occurred in combination with the number

of DDDs dispensed per package dispensed and the number of packages. To account for potentially lower dosages or forgetfulness in older adults, the thus estimated supply was extended as according to a study based on Dutch data (50). Another option would have been to create treatment episodes from cohort entry onwards, again also applying the algorithm developed by Gardarsdottir and Souvereign (50). When lacking more information on prescribed dosage, another option to estimate exposure would have been an investigation of the distribution of the time elapsing between dispensations – the so called waiting time distribution (162, 163), which has recently been further refined for exposure assessment in case-control studies (164). When creating treatment episodes both methods still require some decision-making processes where the supply of one dispensation overlaps the other, i.e. if overlaps should be omitted or if this should partially or fully be considered as stockpiling (208, 209). In both P1 and P3, misclassification of exposure therefore is of concern. However, as estimation of exposure was performed the same way for all patients included in either study, potential bias should be non-differential and for P1, it should have caused rather an underestimation of the effect (210).

Another limitation of the presented studies is the missing of information of OTC drug use (5). For P1, this potentially led to an underassessment of confounding medication, as acetyl salicylic acid and non-steroidal anti-

inflammatory drugs are frequently administered in older adults in Germany and are relevant factors for determining bleeding risks, but in lower dosages which are mainly available OTC. In consequence, residual confounding due incomplete capturing of these drugs may have led to flawed results (211). In P2, a difference in characteristics between off- and on-label users may have been overseen due to the OTC problematic. However, the missing information on OTC medication potentially had the biggest influence on P3. Many preparations of St. John's wort are sold OTC – either at pharmacies or at drug stores – with only the indication, but not the dosage differing between these preparations and prescription preparations of the drug. This had the following consequences: a) the original study presented is not representative of all pregnancies during which St. John's wort is used, as a potentially larger group could not be identified as exposed; and b) misclassification of trimesters as unexposed may have occurred as pregnant women may have bought St. John's wort OTC before or after the first dispensation identified during pregnancy. Misclassification of pregnancies as unexposed during the first trimester though there was a dispensation would have caused a bias towards the null as events are overlooked in this category. At the same time, misclassification of exposure during the second or third trimester as non-exposure would have

resulted in a bias away from the null as the denominator is underestimated.

For all three original studies presented, another limitation is the by and large non-availability of information on lifestyle factors in GePaRD, especially on height, weight, smoking and alcohol consumption (92, 99). Overweight, obesity and smoking are relevant risk factors for the haemorrhagic stroke and are also associated with depression and antidepressant use (67, 68, 212, 213). Information on weight, smoking and alcohol consumption is only included in GePaRD if they are a threat to the patient's overall health and were therefore coded as a disease, i.e. the extremes as obesity and abuse of alcohol and tobacco can be found in GePaRD only. These severe forms would only potentially be identifiable from diagnosis codes describing mental and physical consequences from abusive behaviour. The same applies to illicit drug use. In electronic medical records as secondary, data this information is often available, while it is not available in most claims data such as GePaRD. As a consequence, these lifestyle related factors represent unmeasured confounders in the safety study on the risk of haemorrhagic stroke in antidepressant use. However, by adjusting for diagnoses and other medications associated with these lifestyle-factors, part of the confounding should have been compensated for.

Smoking and alcohol consumption also are risk-factors for occurrence of malformations in babies exposed in utero to St. John's wort (214, 215). Due to the limitations described above, it was therefore not possible to use this information in a meaningful way as potential confounders in the assessment of the relative risk of malformations after 1st trimester exposure to St. John's wort.

For the investigation of pregnancies or pregnant women as a vulnerable group of patients, the lack of more exact information on the gestational age is of a disadvantage compared to studies based on primary data. In primary data studies, the gestational age can be assessed at contact via questionnaire, ultrasound exam or by investigation of medical or maternity records. In secondary data on the other hand, there is some uncertainty as the identification of pregnancies underlies certain assumptions. The identification of pregnancies is based on birth events, screenings and procedures during pregnancy as well as the estimated date of delivery (if available) and the mean duration of pregnancy, while the last menstrual period is unknown (42, 43, 74, 134). For US data, this limitation can potentially partly be resolved in the future, as codes for gestational age were recently introduced to the ICD-10 Clinical Modification (ICD-10-CM) system to be coded when an event during pregnancy cannot be coded ac-

cording to the pregnancy-related chapter of ICD-10-CM (216). Including this information also into the ICD-10-GM would therefore be a great asset.

Despite the disadvantages, there are also some strengths and advantages when investigating the utilization of antidepressants in vulnerable groups of patients based on claims data.

First and foremost, the unselected nature of GePaRD as a study basis facilitates the identification of vulnerable populations, as already demonstrated in previous studies on children, older adults and pregnancies (48, 57, 124, 217-219). Age-based cohorts such as older adults can easily be identified, as certain demographic information including the year of birth are included in GePaRD for almost all patients, with only very few cases of missing or implausible information (92, 99). For pregnant women and also other populations defined by certain markers of health or healthcare utilization, algorithms based on factors that are unique for the respective population can be developed and have been developed to identify the population (43, 134). Moreover, as there are also algorithms available by which mothers and babies can be linked (135), using secondary data as included in GePaRD facilitates investigating the occurrence of malformations, and even of rare malformations (131). The size of GePaRD and its long follow up of currently 16 years (for the original studies included in this dissertation: 8, 11 and 11 years) further facilitates the study of rare

exposures and events generally and also in vulnerable populations, resulting in comparably large cohorts even for subgroups. Furthermore, investigations of trends over longer periods of time, as reported in original studies P2 and P3, can be conducted.

Using secondary data further holds the advantage that both recall and selection bias can be ruled out in the studies conducted (5, 7). As described earlier, it is a known problem in studies based on primary data that people erroneously remember either drug exposure, or the occurrence of a disease during or after therapy, or both. Additionally, when wanting to study the risk of adverse events from drug utilization, it has been shown that there are differences in recall of events between patients having experienced the outcome compared to patients not having experienced the outcome. In consequence, differential misclassification of exposure is of major concern (28, 29, 220, 221). Within the studies conducted for this dissertation, such bias would have been of concern in P1 and P3. In P1, older adults having experienced (and survived) a haemorrhagic stroke would have potentially remembered better which drugs they used at the time of event (28). Similarly, mothers of babies with malformation have been shown to remember differently than mothers of babies without malformations if and when during pregnancy they used medication that potentially may have caused the malformation (221). In studies based on sec-

ondary data, this is not of concern as data collection follows health care provision and diagnosing over time in a uniform manner for all patients. Information on timing of exposure and outcome thus is the same for all patients overall and also within specific groups.

The absence of selection bias is another important advantage of secondary data when studying drug exposure and outcome occurrence. When studying drug safety in antidepressants, secondary data such as claims data or electronic medical records, and GePaRD specifically have the advantage of having a rather complete assessment of drugs prescribed and used. Only OTC medication (and for GePaRD the majority of medication given in hospital) are not captured (7, 92, 99), which in terms of antidepressants is only relevant for St. John's wort. Recall-bias regarding the use of specific drugs and/or the name of the specific drug as seen in primary data studies therefore is not of concern. This is especially relevant in older adults, where recall may be hampered as age-related memory gaps are to be expected.

Furthermore, for all three original studies presented, and especially for P1 and P3, the ability to identify concomitant utilization of potentially interacting drugs is another advantage that secondary data hold. Drug-drug interactions are of special concern in older adults and pregnant women as they might occur at different dosages of drug as well as in different fre-

quencies. However, the knowledge on the safety of antidepressant use per se stemming from clinical trials for older adults and pregnant women in combination with the knowledge that in both groups drugs are metabolized differently compared to younger, healthier, non-pregnant populations in clinical trials is limited (34, 35, 41, 49, 222, 223). Hence, considering the known potentials and further evaluating if these interactions are of relevance in older adults and during pregnancy is another important aspect that can easily be assessed from dispensation data without underlying recall bias for drug exposure.

5. Summary and outlook

Overall, the original studies for this dissertation have shown that real-world data such as GePaRD are an essential resource when studying the utilization of antidepressants in vulnerable groups of patients. Older adults and pregnancies exposed to antidepressants generally and St. John's wort specifically can be identified as comparably large cohorts, enabling the investigation of both infrequent antidepressants as exposure as well as rare outcomes, such as haemorrhagic stroke or specific malformations in babies.

In older adults, the utilization of certain antidepressants leads to an increased risk of stroke due to brain haemorrhage, but the risk differs within classes of antidepressants. This calls for cautious selection of the individual antidepressant to be used, and individual antidepressants of one class therefore should not be treated the same. Generally, prescribing of antidepressants to older adults is not supported by an indicating diagnosis in more than 40% of all prescriptions, with variations between individual antidepressants. Insomnia and pain were identified as two putative indications for OLU of antidepressants, which are licensed indications in certain antidepressants with variations within classes of antidepressants. This suggests that physicians might see indications to be interchangeable between individual antidepressants of one class. As the potential adverse

events from OLU generally are unknown, the high proportion of OLU and the found putative indications call for cautious weighing of benefits and risks when prescribing antidepressants to older adults. During pregnancy, St. John's wort is mainly used during the first trimester, but rarely as an alternative to other antidepressants. In some cases it was used concomitantly with potentially interacting drugs such as antiepileptic drugs, suggesting that awareness of potential drug-drug-interactions needs to be increased. The rate of incomplete pregnancies among pregnancies exposed to St. John's wort is slightly higher than in pregnancies overall identified in GePaRD. As numbers were low, the higher rate of malformations of the heart in babies exposed to St. John's wort during the first trimester needs to be interpreted with caution.

Despite the increased risk for haemorrhagic stroke, further studies need to be conducted as the nested case-control study as a method is not the best choice when wanting to investigate causal contrasts for the utilization of certain antidepressants and the occurrence of the outcome. Hence, the application of other methods to investigate a causal relationship between antidepressant use and the occurrence of haemorrhagic stroke, e.g. by applying the target trial approach would be needed (224, 225).

In older adults, a high proportion of OLU was found. While this may be justified in certain cases, this still holds the potential for unknown ADRs.

Given the scarcity of studies on the risk of ADR due OLU (12, 226) it would be of great relevance to further study the frequency of ADR in off-label antidepressant use in the elderly and comparing the risk of ADR in on-label users and off-label users. An effect of concern would be e.g. the potentially life-threatening serotonin syndrome which is characterized by a combination of symptoms such as hypertension, tremor, tachycardia, agitation and confusion, to name a few (227, 228). It would also be of further interest if the high proportion of OLU can be found overall in adult users of antidepressants in Germany, or if this is only relevant in certain subgroups.

On a more general level, the finding that TCA are the most frequently used class of antidepressants in older adults in Germany also warrants further education for physicians and patients, as safer treatment alternatives among antidepressants are available. TCA seem to be chosen despite their known lower safety and tolerability compared to SSRI and as opposed to practice in other countries where SSRI are the most frequently used antidepressants. This finding also highlights the need to further investigate if the frequent use of TCA is only relevant in older adults, or if TCA are generally still the number one antidepressant group in Germany.

The concomitant use of different antidepressants as well as the concomitant use of antidepressants with potentially interacting drugs are two as-

pects of antidepressant utilization that need to be investigated further. For the simultaneous use of different antidepressants, it is of relevance to identify if this can be seen as a marker of depression that is resistant to single-substance therapy and if e.g. lithium is used for augmentation in these patients. Generally, it needs to be assessed how often antidepressant therapy requires augmentation, and if this is more often the case in older adults compared to adults between ages 18 to 64 years. Concomitant use of antidepressants with potentially interacting drugs needs to be explored further as this may harm success of either one or both therapies and potentially lead to ADR. For this purpose, it would be necessary to explore which interacting drugs are frequently used concomitantly and the occurrence of ADR following this concomitant use. An example would be the use of tamoxifen and certain antidepressants such as paroxetine, where paroxetine leads to partial or full ineffectiveness of tamoxifen with a suspected higher risk of breast cancer recurrence compared to concomitant use of tamoxifen with other non-interacting antidepressants.

For studies on the risk of ADR in general and in relation to drug-drug interactions specifically, it would be beneficial to have more information on the use of OTC medication, especially acetyl salicylic acid and non-steroidal anti-inflammation drugs (NSAIDs) such as low-dose ibuprofen, and – if possible – also on the metabolizer status of patient. While the

former would be relevant as both confounders and potentially interacting drugs, the metabolizer status could help improve exposure estimations and enable to consider this information when assessing the risk for an ADR due to drug-drug interactions. For exposure estimation, the metabolizer status could help optimizing estimations by e.g. explaining seemingly implausible gaps between dispensations due to lower dosages being used and thus less frequent prescriptions being needed. Information if a patient is a low metabolizer would be helpful in drug-drug interaction studies, as this would enable subgroup analysis and thus the identification of special risks due to drugs being processed at a slower rate. A potential source for this information could be e.g. the data from the NAKO-Gesundheitsstudie where all drugs used during the past seven days are assessed, and where metabolizer status could be identified from blood samples drawn. For part of the volunteers included in the NAKO study, this information could be directly linked to GePaRD.

Regarding the use of St. John's wort during pregnancy and a potentially increased risk for cardiac malformations after first trimester exposure, different steps could be taken in the future. Internationally, it could be explored which other databases hold information on both pregnancy and the use of St. John's wort. Within GePaRD, finding suitable active comparators as well as potential study designs would be needed to further inves-

tigate the increased relative risk of cardiac malformations after first trimester exposure.

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Appendix A.

Classification of antidepressants[1]

ATC-code[2]	Substance	Classification
N06AA01	Desipramine	TCA
N06AA02	Imipramine	TCA
N06AA04	Clomipramine	TCA
N06AA05	Opipramol	TCA
N06AA06	Trimipramine	TCA
N06AA07	Lofepramine	TCA
N06AA08	Dibenzipin	TCA
N06AA09	Amitriptyline	TCA
N06AA10	Nortriptyline	TCA
N06AA12	Doxepin	TCA
N06AA16	Dosulepin	TCA
N06AA21	Maprotiline	TCA
N06AA25	Amitriptylinoxide	TCA
N06AB03	Fluoxetine	SSRI
N06AB04	Citalopram	SSRI
N06AB05	Paroxetine	SSRI
N06AB06	Sertraline	SSRI
N06AB08	Fluvoxamine	SSRI
N06AB10	Escitalopram	SSRI
N06AF04	Tranylcypromine	MAO
N06AG02	Moclobemide	MAO
N06AH01	St. John's wort	Herbal antidepressants
N06AH10	Homoeopathic antidepressants	Herbal antidepressants
N06AP01	St. John's wort	Herbal antidepressants
N06AP51	St. John's wort, combinations	Herbal antidepressants
N06AX02	Tryptophan	Other antidepressants
N06AX03	Mianserin	NaSSA
N06AX05	Trazodone	Other antidepressants
N06AX09	Viloxazine	NARI
N06AX11	Mirtazapine	NaSSA
N06AX12	Bupropion	Other antidepressants

[1] Only antidepressants with their respective ATC-codes that are/were authorized in Germany since 2004 and for which a dispensation was found in GePaRD are listed.

[2] According to the ATC classification by the "Wissenschaftliche Institut der Ortskassen" (WIdO)

N06AX14	Tianeptine	Other antidepressants
N06AX16	Venlafaxine	SSNRI
N06AX18	Reboxetine	NARI
N06AX21	Duloxetine	SSNRI
N06AX22	Agomelatine	Other antidepressants
N06AX26	Vortiotexin	Other antidepressants

Appendix B.

Examples of reimbursable preparations of St. John's wort included in GePaRD

ATC	ATC Bedeutung	Artikelname	Darreichungsform	Wirkstoff	Wirkstoffmenge	Einheit
N06AP01	Johanniskraut	FELIS 425 mg Hartkapseln	Hartkapseln	Johanniskraut-Trockenextrakt (3,5-6:1); Auszugsmittel: Ethanol 60% (m/m)	425	mg
N06AP01	Johanniskraut	FELIS 425 mg Hartkapseln	Hartkapseln	Johanniskraut-Trockenextrakt (3,5-6:1); Auszugsmittel: Ethanol 60% (m/m)	425	mg
N06AP01	Johanniskraut	FELIS 425 mg Hartkapseln	Hartkapseln	Johanniskraut-Trockenextrakt (3,5-6:1); Auszugsmittel: Ethanol 60% (m/m)	425	mg
N06AP01	Johanniskraut	FELIS 650 Film-tabletten	Filmtabletten	Johanniskraut-Trockenextrakt (3,5-6:1); Auszugsmittel:	650	mg

				Ethanol 60% (m/m)		
N06AP01	Johanniskraut	FELIS 650 mg Filmtabletten	Filmtabletten	Johanniskraut-Trockenextrakt (3,5-6:1); Auszugsmittel: Ethanol 60% (m/m)	650	mg
N06AP01	Johanniskraut	FELIS 650 mg Filmtabletten	Filmtabletten	Johanniskraut-Trockenextrakt (3,5-6:1); Auszugsmittel: Ethanol 60% (m/m)	650	mg
N06AP01	Johanniskraut	JARSIN 300 überzogene Tabletten	Überzogene Tabletten	Johanniskraut-Trockenextrakt (3-6:1); Auszugsmittel: Methanol 80% (V/V)	300	mg
N06AP01	Johanniskraut	JARSIN 300 überzogene Tabletten	Überzogene Tabletten	Johanniskraut-Trockenextrakt (3-6:1); Auszugsmittel: Methanol 80% (V/V)	300	mg
N06AP01	Johanniskraut	JARSIN 450 mg überzogene Tabletten	Überzogene Tabletten	Johanniskraut-Trockenextrakt (3-6:1); Auszugsmittel: Methanol 80% (V/V)	450	mg

N06AP01	Johanniskraut	JARSIN 450 mg überzogene Tabletten	Überzogene Tabletten	Johanniskraut-Trockenextrakt (3-6:1); Auszugsmittel: Methanol 80% (V/V)	450	mg
N06AP01	Johanniskraut	JARSIN 450 mg überzogene Tabletten	Überzogene Tabletten	Johanniskraut-Trockenextrakt (3-6:1); Auszugsmittel: Methanol 80% (V/V)	450	mg
N06AP01	Johanniskraut	JARSIN 750 mg Tabl.ueberzogen	Überzogene Tabletten	Johanniskraut-Trockenextrakt (3-6:1); Auszugsmittel: Methanol 80% (V/V)	750	mg
N06AP01	Johanniskraut	JARSIN 750 mg Tabl.ueberzogen	Überzogene Tabletten	Johanniskraut-Trockenextrakt (3-6:1); Auszugsmittel: Methanol 80% (V/V)	750	mg
N06AP01	Johanniskraut	JARSIN 750 mg Tabl.ueberzogen	Überzogene Tabletten	Johanniskraut-Trockenextrakt (3-6:1); Auszugsmittel: Methanol 80% (V/V)	750	mg
N06AP01	Johanniskraut	JARSIN RX 300	Überzogene Tablet-	Johanniskraut-	300	mg

		mg überzogene Tabletten	ten	Trockenextrakt (3-6:1); Auszugsmittel: Methanol 80% (V/V)		
N06AP01	Johanniskraut	JARSIN RX 300 mg überzogene Tabletten	Überzogene Tabletten	Johanniskraut-Trockenextrakt (3-6:1); Auszugsmittel: Methanol 80% (V/V)	300	mg
N06AP01	Johanniskraut	JARSIN RX 300 mg überzogene Tabletten	Überzogene Tabletten	Johanniskraut-Trockenextrakt (3-6:1); Auszugsmittel: Methanol 80% (V/V)	300	mg
N06AP01	Johanniskraut	JOHANNISKRAUT AL Hartkapseln	Hartkapseln	Johanniskraut-Trockenextrakt (3,5-6:1); Auszugsmittel: Ethanol 60% (m/m)	425	mg
N06AP01	Johanniskraut	JOHANNISKRAUT AL Hartkapseln	Hartkapseln	Johanniskraut-Trockenextrakt (3,5-6:1); Auszugsmittel: Ethanol 60% (m/m)	425	mg
N06AP01	Johanniskraut	JOHANNISKRAUT SANDOZ 425 mg	Hartkapseln	Johanniskraut-Trockenextrakt (3,5-	425	mg

		Hartkapseln		6:1); Auszugsmittel: Ethanol 60% (m/m)		
N06AP01	Johanniskraut	JOHANNIS-KRAUT-CT Hart-kapseln	Hartkapseln	Johanniskraut-Trockenextrakt (3,5-6:1); Auszugsmittel: Ethanol 60% (m/m)	425	mg
N06AP01	Johanniskraut	JOHANNIS-KRAUT-RATIOPHARM 425 mg Hartkaps.	Kapseln	Johanniskraut-Trockenextrakt (3,5-6:1); Auszugsmittel: Ethanol 60% (m/m)	425	mg
N06AP01	Johanniskraut	JOHANNIS-KRAUT-RATIOPHARM 425 mg Hartkaps.	Kapseln	Johanniskraut-Trockenextrakt (3,5-6:1); Auszugsmittel: Ethanol 60% (m/m)	425	mg
N06AP01	Johanniskraut	KIRA 300 mg überzogene Tab-letten	Überzogene Tablet-ten	Johanniskraut-Trockenextrakt (3-6:1); Auszugsmittel: Metha-nol 80% (V/V)	300	mg
N06AP01	Johanniskraut	KIRA 300 mg überzogene Tab-letten	Überzogene Tablet-ten	Johanniskraut-Trockenextrakt (3-6:1); Auszugsmittel: Metha-	300	mg

				nol 80% (V/V)		
N06AP01	Johanniskraut	LAIF 600 Tablet-ten	Tabletten	Johanniskraut-Trockenextrakt (5-8:1); Auszugsmittel: Ethanol 50% (V/V)	612	mg
N06AP01	Johanniskraut	LAIF 600 Tablet-ten	Tabletten	Johanniskraut-Trockenextrakt (5-8:1); Auszugsmittel: Ethanol 50% (V/V)	612	mg
N06AP01	Johanniskraut	LAIF 600 Tablet-ten	Tabletten	Johanniskraut-Trockenextrakt (5-8:1); Auszugsmittel: Ethanol 50% (V/V)	612	mg
N06AP01	Johanniskraut	LAIF 900 Balance Filmtabletten	Filmtabletten	Johanniskraut-Trockenextrakt (3-6:1); Auszugsmittel: Ethanol 80% (V/V)	900	mg
N06AP01	Johanniskraut	LAIF 900 Balance Filmtabletten	Filmtabletten	Johanniskraut-Trockenextrakt (3-6:1); Auszugsmittel: Ethanol 80% (V/V)	900	mg

N06AP01	Johanniskraut	LAIF 900 Filmtabletten	Filmtabletten	Johanniskraut-Trockenextrakt (3-6:1); Auszugsmittel: Ethanol 80% (V/V)	900	mg
N06AP01	Johanniskraut	LAIF 900 Filmtabletten	Filmtabletten	Johanniskraut-Trockenextrakt (3-6:1); Auszugsmittel: Ethanol 80% (V/V)	900	mg
N06AP01	Johanniskraut	LAIF 900 Tabletten	Tabletten	Johanniskraut-Trockenextrakt (3-6:1); Auszugsmittel: Ethanol 80% (V/V)	900	mg
N06AP01	Johanniskraut	NEUROPLANT 1x1 Filmtabl.	Filmtabletten	Johanniskraut-Trockenextrakt	600	mg
N06AP01	Johanniskraut	NEUROPLANT 1x1 Filmtabl.	Filmtabletten	Johanniskraut-Trockenextrakt	600	mg
N06AP01	Johanniskraut	NEUROPLANT 1x1 Filmtabl.	Filmtabletten	Johanniskraut-Trockenextrakt	600	mg
N06AP01	Johanniskraut	NEUROPLANT 300 mg N Filmtabl.	Filmtabletten	Johanniskraut-Trockenextrakt (4-7:1); Auszugsmittel: Metha-	300	mg

				nol 80% (V/V)		
N06AP01	Johanniskraut	NEUROPLANT aktiv Filmtabletten	Filmtabletten	Johanniskraut-Trockenextrakt (3-7:1); Auszugsmittel: Methanol 80% (V/V)	600	mg
N06AP01	Johanniskraut	NEUROPLANT aktiv Filmtabletten	Filmtabletten	Johanniskraut-Trockenextrakt (3-7:1); Auszugsmittel: Methanol 80% (V/V)	600	mg
N06AP01	Johanniskraut	NEUROPLANT aktiv Filmtabletten	Filmtabletten	Johanniskraut-Trockenextrakt (3-7:1); Auszugsmittel: Methanol 80% (V/V)	600	mg
N06AP01	Johanniskraut	NEUROPLANT aktiv Filmtabletten	Filmtabletten	Johanniskraut-Trockenextrakt (3-7:1); Auszugsmittel: Methanol 80% (V/V)	600	mg
N06AP01	Johanniskraut	NEUROPLANT Filmtabletten	Filmtabletten	Johanniskraut-Trockenextrakt (3-7:1); Auszugsmittel: Methanol 80% (V/V)	600	mg

N06AP01	Johanniskraut	NEUROPLANT Filmtabletten	Filmtabletten	Johanniskraut-Trockenextrakt (3-7:1); Auszugsmittel: Methanol 80% (V/V)	600	mg
N06AP01	Johanniskraut	NEUROPLANT Filmtabletten	Filmtabletten	Johanniskraut-Trockenextrakt (3-7:1); Auszugsmittel: Methanol 80% (V/V)	600	mg
N06AP01	Johanniskraut	NEUROPLANT Filmtabletten	Filmtabletten	Johanniskraut-Trockenextrakt (3-7:1); Auszugsmittel: Methanol 80% (V/V)	600	mg
N06AP01	Johanniskraut	REMOTIV Filmtabletten	Filmtabletten	Johanniskraut-Trockenextrakt (4-7:1); Auszugsmittel: Ethanol 50% (m/m)	250	mg
N06AP01	Johanniskraut	SPILAN 425 mg Hartkapseln	Hartkapseln	Johanniskraut-Trockenextrakt (3,5-6:1); Auszugsmittel: Ethanol 60% (m/m)	425	mg
N06AP01	Johanniskraut	TEXX 300 Film-	Filmtabletten	Johanniskraut-	300	mg

		tabletten		Trockenextrakt (4-7:1); Auszugsmittel: Metha-nol 80% (V/V)		
N06AP01	Johanniskraut	TEXX 300 Film-tabletten	Filmtabletten	Johanniskraut-Trockenextrakt (4-7:1); Auszugsmittel: Metha-nol 80% (V/V)	300	mg

Appendix C. P1

Schäfer, W., Princk, C., Kollhorst, B. et al. Antidepressants and the Risk of Hemorrhagic Stroke in the Elderly: a Nested Case–Control Study. Drug Saf 42, 1081–1089 (2019). https://doi.org/10.1007/s40264-019-00837-y

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ORIGINAL RESEARCH ARTICLE

Antidepressants and the Risk of Hemorrhagic Stroke in the Elderly: a Nested Case–Control Study

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Abstract

Background and Purpose Selective serotonin reuptake inhibitors (SSRIs) are frequently prescribed in the elderly due to a more favorable risk profile than other antidepressants (ADs). However, SSRIs are associated with an increased risk of gastrointestinal bleeding, while evidence on the risk of hemorrhagic stroke (HS) is limited. Therefore, we compared the risk of HS associated with the use of ADs in the elderly.

Methods Based on data from the German Pharmacoepidemiological Research Database (GePaRD), a case–control study matched on age, sex, and health insurance provider, nested in a cohort of incident users of ADs ≥ 65 years of age was performed. Cases were identified from hospital discharge diagnoses, and exposure was identified from outpatient prescriptions. Multivariable conditional logistic regression was used to estimate adjusted odds ratios (ORs) with 95% confidence intervals (CIs).

Results Based on 4059 cases and 40,590 controls, an increased risk of HS was found in current use of SSRIs (OR 1.39, 95% CI 1.22–1.58), selective serotonin and noradrenaline reuptake inhibitors (1.69, 1.35–2.11), noradrenergic and specific serotonergic ADs (1.44, 1.22–1.69), and noradrenaline reuptake inhibitors (3.81, 1.54–9.43) compared with tri- and tetracyclic antidepressants. An increased risk of HS was seen in patients with a high baseline risk of bleeding and in patients with depression. The risk of HS varied between individual ADs.

Conclusion Our study shows that the use of medications inhibiting serotonin and/or noradrenaline reuptake increases the risk of HS in patients aged 65 years and older and that the risk varies across individual ADs.

Key Points

The risk for hemorrhagic stroke is increased in elderly users of selective serotonin reuptake inhibitors, selective serotonin and noradrenaline reuptake inhibitors, noradrenergic and specific serotonergic antidepressants and noradrenaline reuptake inhibitors compared with tri- and tetracyclic antidepressants, and varies across individual antidepressants.

The risk is higher in patients with depression and a higher baseline risk of bleeding, but for some AD classes, the risks are also elevated in patients with a low baseline risk of bleeding.

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1 Introduction

In patients aged 65 years or older, antidepressants (ADs), especially tri- and tetracyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs), are frequently prescribed for the treatment of depressive disorders [1]. SSRIs are usually preferred to TCAs due to a more favorable risk profile in the treatment of the elderly [2, 3]; however, over the past two decades, studies have shown that the use of SSRIs is associated with an increased risk of gastrointestinal and other bleeding events [4–6]. One of the most serious bleeding events is hemorrhagic stroke (HS), which has a high fatality, especially within the first 30 days after diagnosis [7, 8]. Depending on the damage caused to the brain, patients might never fully recover, leading to disability and associated high costs and loss of quality of life [9].

Several studies examined the risk of HS [10–12] or intracranial hemorrhage [13–16] associated with the use of SSRIs. However, in their systematic review, Douros et al. showed that most of these studies suffered from methodological problems (e.g. inclusion of prevalent users rather

than incident users) or lack of power [17]. They summarized that no firm conclusions could be drawn based on the existing studies and that further research was needed [17], although some studies indicated an increased risk of HS associated with the use of ADs [12, 16, 18, 19]. We addressed the methodological issues by performing a case–control analysis in a cohort of more than 700,000 incident AD users and selecting TCAs as the active comparator, and focused on older patients. The aim of this study was to compare the risk of HS between different classes of ADs, as well as between individual agents.

2 Materials and Methods

2.1 Data Source

This study is based on data from the German Pharmacoepidemiological Research Database (GePaRD), which is based on claims data from four statutory health insurance providers (SHIs) in Germany and currently includes information on more than 20 million persons who have been insured with one of the participating providers since 2004 or later. In addition to demographic data, the GePaRD contains information on all reimbursable outpatient drug dispensations and all reimbursable outpatient (i.e. from general practitioners and specialists) and inpatient diagnoses and services. Diagnoses are coded according to the International Classification of Diseases, 10th revision, German modification (ICD-10-GM). Per data year, information is available on approximately 17% of the general population, and all geographical regions of Germany are represented. Methodological assessment and validation studies have shown the applicability of the GePaRD for pharmacoepidemiological research, and the GePaRD has been used for various pharmacoepidemiological studies [20–22].

2.2 Study Design and Setting

The study was conducted as a case–control study nested in a population-based cohort of incident AD users between 1 January 2005 and 31 December 2011. An incident user design was selected to avoid bias related to the depletion of susceptibles and under-ascertainment of early adverse effects [23]. To enter the cohort, patients had to (1) be aged 65 years or older; (2) be insured continuously for at least 365 days before cohort entry; and (3) receive their first outpatient AD prescription after 365 days, without a prescription for an AD. Patients with a history of HS were not excluded. Cohort entry was the first day all criteria were fulfilled, while cohort exit was defined as (1) interruption of the insurance status for more than 3 days or end of insurance, including death; (2) end of the study period; or (3) the occurrence of HS, whichever came first.

2.3 Case Definition and Control Selection

Cases of HS were identified by main hospital discharge diagnoses indicating subarachnoid bleeding, intracerebral bleeding, or non-traumatic intracranial bleeding not coded as epidural or subdural (ICD-10-GM codes I60, I61, and I62.9). In sensitivity analyses, two more specific case definitions were used, excluding (1) cases without imaging procedures performed 2 days before to 2 days after the index day, or (2) cases with an acute traumatic brain injury (ICD-10-GM code S06) in the 30 days before the index day. In the second sensitivity analysis, we also excluded controls with an acute traumatic brain injury in the 30 days before the index day.

The index day was set to the admission date of the respective hospitalization. Up to 10 controls were matched to each case by sex, year of birth (±1 year), and SHI, using risk set sampling with time in cohort as the time axis. The date resulting in the same time of follow-up as for the respective case was designated as the index date of the control. Eligible patients hospitalized for any reason at the index date of the case were not at risk of being hospitalized for HS and were thus excluded from the set of potential controls. Cases were eligible to be selected as a control before their index day and controls could be selected more than once [24].

2.4 Exposure Definition

Dispensations of ADs were identified through the Anatomical Therapeutic Chemical (ATC) classification system code N06A, and classified according to their proposed mode of action: TCAs, SSRIs, monoamine oxidase inhibitors (MAOs), selective serotonin noradrenaline reuptake inhibitors (SSNRIs), noradrenaline reuptake inhibitors (NARIs), noradrenergic and specific serotonergic antidepressants (NaSSAs), Hypericum St. John's wort and homeopathic ADs (herbal), and other ADs (other). As in previous studies [22, 25], supply was estimated as the amount of defined daily doses (DDDs) of the dispensation plus an additional 150% of the DDD to account for lower dosage and lack of compliance in the elderly [26, 27]. In sensitivity analyses, supply was estimated as (1) number of DDDs, and (2) four times the number of DDDs (= adding 300% of the DDDs). Taking into consideration the long half-life of several ADs, the end of the exposure period was defined as the end of supply plus a 30-day carryover period. Based on the period between the end of the exposure period of the last dispensation and the index day, exposure status was defined as (1) current if

the exposure period overlapped the index day; (2) recent if the exposure period ended 1–30 days before the index day; and (3) past if the exposure period ended more than 30 days before the index day. Current users of two or more ADs of different classes (class-level analysis) or of individual agents (agent-level analysis) were assigned to the separate category 'multiple use'.

2.5 Assessment of Potential Confounders

Comorbidities including risk factors for HS were obtained from in- and outpatient diagnoses in the 365 days before cohort entry. History of medication serving as a proxy for the severity of disease and overall health status was retrieved from outpatient drug dispensation data in the 365 days before cohort entry. Additionally, the use of potential confounding drugs was assessed by searching for dispensations of the respective drugs with supplies overlapping the index day.

To identify patients with a high risk of bleeding and to assess possible effect modification by the baseline bleeding risk, the HAS-BLED score by Pisters et al. [28] was calculated using patient information at cohort entry. Information on the international normalized ratio is not available in the GePaRD and was therefore not used for the calculation.

2.6 Statistical Analysis

Conditional logistic regression was used to estimate matched and adjusted odds ratios (ORs) with 95% confidence intervals (95% CIs), comparing current, recent, and past use of AD classes with current use of TCAs, and current use of individual agents with current use of amitriptyline. TCAs and amitriptyline were chosen as the reference as they have not been associated with bleeding events thus far and represented the most frequently prescribed ADs in the underlying cohort [29].

Risk factors of HS, as well as comorbidities, comedications, indicators of lifestyle habits, and indicators of overall health status were taken into account as potential confounders. Predefined confounders, e.g. a history of HS, congestive heart failure, use of antiarrhythmic drugs or antihypertensive drugs at baseline, were always included in the model. A backward selection procedure (Wald test p value < 0.05 for staying in the model) was used to select further relevant covariates. In a sensitivity analysis, a full model, including all potential confounders, was calculated. Additionally, stratified analyses were performed for an HAS-BLED score ≥ 3 (yes/no), diagnosis of depression (yes/no), and diagnosis of depression but no diagnosis of cancer or pain (yes/no). All statistical analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

3 Results

Overall, 714,444 incident AD users were included. During the study period, 4059 cases of HS were observed. The mean time between cohort entry and onset of stroke was 832 days (standard deviation 648). The overall incidence rate (IR) of HS in the cohort was 1.7 (95% CI 1.6–1.7) per 1000 person-years (PYs), with the highest (unadjusted) IR seen in patients starting use of an SSRI (2.3, 2.2–2.4) and the lowest in patients starting use of a TCA (1.5, 1.4–1.5).

All 4059 cases could be matched to 10 controls. Approximately two-thirds (67.5%) of the cases were female and the median age was 78 years (25–75% quantile, 73–83 years). Overall, risk factors of HS and other comorbidities were a bit more frequent in cases, while use of drugs other than ADs at index day was more frequent in controls (see Table 1).

Compared with current TCA use, an elevated risk for HS was seen for current use of SSRIs (adjusted OR 1.39, 95% CI 1.22–1.58), SSNRIs (1.69, 1.35–2.11), NaSSAs (1.44, 1.22–1.69), and NARIs (3.81, 1.54–9.43), whereas a lower risk was seen in current use of MAOs (0.55, 0.28–1.05) (see Table 2). The ORs were similar when the more specific case definitions were applied, considering only cases with imaging procedures for diagnosis (sensitivity analysis 1) or only cases (and controls) without traumatic brain injury in the 30 days before index day (sensitivity analysis 2) (for both analyses, see Table 3).

For SSRIs, SSNRIs, NaSSAs and NARIs, an increased risk of HS compared with TCA use was seen in current users with a high baseline risk of bleeding, i.e. an HAS-BLED score value of 3 or more (see electronic supplementary material 1). An increased risk of HS was also observed in current users of SSRIs, SSNRIs, NaSSAs and NARIs with a low baseline risk of bleeding.

In patients with depression, an increased risk of HS was seen for current use of SSRIs, SSNRIs, NaSSAs and NARIs compared with TCAs (see electronic supplementary material 2). By restricting the analysis further to patients with a diagnosis of depression but no diagnosis of cancer or pain, an increased risk was observed for SSRIs, SSNRIs, NARIs and NaSSAs.

The estimated effects were robust to changes of the definition of supply in all AD classes presented, except for NARIs, where the estimate was smaller when the supply was estimated as the number of DDDs only. Results of these sensitivity analyses are shown in electronic supplementary material 3.

Compared with current use of amitriptyline, a higher risk for HS was seen in current use of the TCAs amitriptylinoxide (OR 2.55, 95% CI 1.36–4.77), clomipramine (1.88, 0.93–3.79), maprotiline (3.23, 1.75–5.96), and nortriptyline (3.46, 1.66–7.24); the SSRIs escitalopram (2.12, 1.49–3.01) and citalopram (1.30, 1.07–1.57); the SSNRI venlafaxine (2.17, 1.59–2.95); the NaSSA mirtazapine (1.24, 1.01–1.52);

Table 1 Characteristics of cases with hemorrhagic stroke, and matched controls

	Cases [*n*=4059] (%)	Controls [*n*=40,590] (%)	Adjusted OR (95% CI)
Female	2738 (67.5)	27,380 (67.5)	
Median age at index date, years [Q1–Q3]	78 [73–83]	78 [73–83]	
History of:			
Depression[a]	2224 (54.8)	21,392 (52.7)	1.19 (1.10–1.29)
Intracerebral, intracranial or subarachnoid bleeding[a]	456 (11.2)	538 (1.3)	5.02 (34.22–5.97)
Gastrointestinal bleedings[a]	81 (2.0)	535 (1.3)	2.22 (1.66–2.97)
Congestive heart failure[a]	941 (23.2)	7637 (18.8)	1.23 (1.11–1.36)
Hypertension[a]	3207 (79.0)	31,232 (76.9)	0.95 (0.86–1.04)
Ischemic stroke and TIA[a]	1011 (24.9)	4449 (11.0)	1.80 (1.61–2.01)
Myocardial infarction[a]	234 (5.8)	2808 (6.9)	0.90 (0.76–1.08)
Coronary heart disease[a]	1347 (33.2)	13,311 (32.8)	1.11 (1.01–1.22)
Vascular diseases[a,c]	1373 (33.8)	11,520 (28.4)	1.34 (1.23–1.47)
Cancer	867 (21.4)	8312 (20.5)	0.84 (0.76-0.92)
Pain	2126 (52.4)	21,847 (53.8)	1.41 (1.31–1.53)
Dementia	1159 (28.5)	6610 (16.3)	1.24 (1.08–1.42)
Cardiac arrhythmia	1347 (33.2)	12,262 (30.2)	1.26 (1.16–1.37)
Epilepsy	1387 (34.2)	10,338 (25.5)	1.92 (1.76-2.09)
Other neurological disorders[d]	380 (9.4)	1196 (2.9)	1.51 (1.27–1.78)
Parkinson's disease and movement disorders	1201 (25.6)	10,589 (26.1)	1.14 (1.04-1.25)
Renal diseases	710 (17.5)	6009 (14.8)	–[b]
COPD	948 (23.4)	10,799 (26.2)	0.91 (0.83–1.00)
Diabetes	1277 (31.5)	10,954 (27.0)	1.20 (1.11–1.31)
Obesity	527 (13.0)	6161 (15.2)	–[b]
Signs for malnutrition (fluid and electrolyte deficit and deficiency anemia)	772 (19.0)	4875 (12.01)	1.21 (1.08–1.35)
Drug use at baseline			
Angiotensin II receptor blockers	1071 (26.4)	10,339 (25.5)	–[b]
Calcium channel inhibitors	1967 (51.5)	16,629 (41.0)	1.54 (1.41–1.67)
Diuretics	1373 (33.8)	13,488 (33.2)	–[b]
Vasodilators	976 (24.1)	11,168 (27.5)	–[b]
Other antihypertensive drugs[e]	2484 (61.2)	23,588 (58.1)	–[b]
Glucocorticosteroids	1098 (27.1)	13,164 (32.4)	1.25 (1.14–1.36)
Antidementive drugs	683 (16.8)	3539 (8.7)	1.68 (1.43–1.96)
Drug use at index date			
Acetylsalicylic acid[a,f]	28 (0.7)	1153 (2.8)	0.25 (0.15–0.40)
Antithrombotic agents[a,g]	1106 (27.2)	20,460 (50.4)	0.33 (0.30–0.36)
Nonsteroidal anti-inflammatory drugs[a]	438 (10.8)	24,712 (60.9)	0.06 (0.06–0.07)

OR odds ratio, *CI* confidence interval, *TIA* transient ischemic attack, *COPD* chronic obstructive pulmonary disease, *ATC* Anatomical Therapeutic Chemical, *NOAC* novel oral anticoagulant

[a]A priori variable, always included in the model

[b]Variable removed by backward selection

[c]Defined as peripheral vascular disease, stenosis of the carotid artery, venous thromboembolism and valvular diseases

[d]Includes Huntington's disease (G10), hereditary ataxia (G11), spinal muscular atrophy (G12), systemic atrophies (G13), postpolio syndrome (G14), drug-induced chorea (G25.4), other chorea (G25.5), degeneration of nervous system due to alcohol (G31.2), other specified and unspecified degenerative diseases of nervous system (G31.8 and G31.9), other degenerative disorders of nervous system in diseases classified elsewhere (G32), multiple sclerosis (G35), other acute disseminated demyelination (G36), other demyelinating diseases of central nervous system (G37), speech disturbances not elsewhere classified (R47) and convulsions not elsewhere classified (R56)

[e]C02K

[f]As analgesic or antipyretic (N02BA01)

[g]ATC group B01A antithrombotic agents, i.e. vitamin K antagonists (B01AA), heparin (B01AB), platelet aggregation inhibitors (B01AC), enzymes (B01AD), direct thrombin (B01AE) and factor Xa inhibitors (B01AF) (=NOACs), and other antithrombotic agents (B01AX)

Table 2 Matched and adjusted odds ratios for the risk of hemorrhagic stroke in current antidepressant use compared with current TCA use

Class of AD (*N* cases/controls)	Matched OR		Adjusted OR Main analysis [*n* cases: 4059]	
	OR	CI	OR	CI
TCA (723/8413)	1.00 (Ref).	– (Ref)	1.00 (Ref)	– (Ref)
SSRI (800/5209)	1.79	1.61–2.00	**1.39**	**1.22–1.58**
SSNRI (139/1271)	1.24	1.02–1.51	**1.69**	**1.35–2.11**
NaSSA (354/2629)	1.56	1.37–1.79	**1.44**	**1.22–1-69**
NARI (11/26)	5.45	2.68–11.08	**3.81**	**1.54–9.43**
MAO (12/220)	0.64	0.35–1.14	0.55	0.28–1.05

Adjusted for the variables listed in Table 1

Estimates for the use of multiple and other ADs, as well as herbal ADs, are not presented as these drugs are only reimbursed in very selected patients and numbers were very small

Bold values indicate estimates with a CI not overlapping the null value "1"

OR odds ratio, *AD* antidepressant, *CI* confidence interval, *TCA* tri- and tetracyclic antidepressant, *SSRI* selective serotonin reuptake inhibitor, *SSNRI* selective serotonin noradrenaline reuptake inhibitor, *NaSSA* noradrenergic and specific serotonergic antidepressant, *NARI* noradrenaline reuptake inhibitor, *MAO* monoamine oxidase inhibitor

Table 3 Adjusted odds ratios for the risk of hemorrhagic stroke in current antidepressant use compared with current TCA use: sensitivity analysis regarding the case definition

Class of AD	Adjusted OR Sensitivity 1[a]			Adjusted OR Sensitivity 2[b]		
	N cases/controls	OR	CI	*N* cases/controls	OR	CI
TCA	618/7123	1.00 (Ref)	– (Ref)	702/8172	1.00 (Ref)	– (Ref)
SSRI	669/4329	**1.37**	**1.19–1.57**	778/5073	**1.53**	**1.08–2.17**
SSNRI	117/1105	**1.58**	**1.25–2.01**	137/1248	**2.66**	**1.44–4.93**
NaSSA	299/2218	**1.43**	**1.20–1.71**	343/2554	1.40	0.90–2.17
NARI	9/21	**3.76**	**1.38–10.20**	10/26	3.63	0.36-36.56
MAO	9/188	0.47	0.22–0.98	12/212	0.93	0.20–4.43

Adjusted for the variables listed in Table 1

Bold values indicate estimates with a CI not overlapping the null value "1"

OR odds ratio, *AD* antidepressant, *CI* confidence interval, *TCA* tri- and tetracyclic antidepressant, *SSRI* selective serotonin reuptake inhibitor, *SSNRI* selective serotonin noradrenaline reuptake inhibitor, *NaSSA* noradrenergic and specific serotonergic antidepressant, *NARI* noradrenaline reuptake inhibitor, *MAO* monoamine oxidase inhibitor

[a]Only cases with imaging procedures 2 days before to 2 days after the index day

[b]Exclusion of cases with a diagnosis of traumatic brain injury within 30 days before the index day

and the NARI reboxetine (3.07, 1.21–7.77). Lower risks of HS were seen for current use of the TCAs doxepine (0.62, 0.49–0.79) and trimipramine (0.50, 0.37–0.67); the SSRI paroxetine (0.71, 0.49–1.04); and the MAO moclobemide (0.46, 0.21–1.00). Figure 1 shows the risk of HS in current use of individual ADs compared with amitriptyline.

4 Discussion

In this large population-based study including more than 700,000 incident elderly users of ADs, we showed that current use of SSRIs (1.39, 1.22–1.58), SSNRIs (1.69, 1.35–2.11), NaSSAs (1.44, 1.22–1.69), and NARIs (3.81, 1.54–9.43), i.e. ADs inhibiting serotonin and/or noradrenaline reuptake, was associated with an increased risk of HS compared with current use of TCAs. Further investigations revealed that the risk varied across individual ADs. Taking into account a wide range of comorbidities, use of comedications, and other potential confounding factors, the highest risk estimate was seen for the TCA amitriptylinoxide and the NARI reboxetine, but, in addition, the widely used TCAs clomipramine, nortriptyline, and maprotiline, and the SSRI escitalopram, were associated with a twofold higher risk of HS. Despite the observed increases in risk, HS remains a rare event, with 4059 cases among 714,444 new users of ADs (0.57%) and IRs ranging between 1.5 and 2.3 per 1000

PYs. It also still remains a less frequent event than, for example, gastrointestinal bleedings [18].

Our results are in line with those of Renoux et al., who observed, in the general adult population, a relative risk of intracranial hemorrhage of 1.17 for SSRIs compared with TCAs [16]; the systematic review by Douros et al., also focusing on the general adult population [17]; and Lee et al. [30], who observed a hazard ratio of 1.17 for SSNRIs compared with SSRIs. Comparison with other studies is hampered by the inclusion of prevalent users [13, 18, 31] and other methodological problems [17]. Regarding individual agents, we identified only one study that investigated the risk of stroke in the elderly; however, as the authors of that study were not able to distinguish between ischemic and hemorrhagic stroke, leading to the possibility that the majority of identified cases of stroke were ischemic and not hemorrhagic, comparison was difficult [32].

As in all observational studies, confounding by indication is of concern, especially as ADs are not only used for the treatment of depression but also for other indications, such as (cancer-related or neuropathic) pain [33]. Additionally, indications may overlap; for example, sleep disturbances are commonly associated with depression in the elderly. To account for different indications and resulting possible differences in dosage, we adjusted for depression as well as potential other indications. Furthermore, we examined the risk of HS in a more homogeneous group of patients with a diagnosis of depression, and the even further restricted group of patients with depression but no diagnosis of pain or cancer. In these analyses, the estimated effects were larger for SSRIs, SSNRIs and NaSSA, indicating that the higher risks seen for these AD classes cannot just be explained by confounding by indication. However, the risks were smaller for NARIs, suggesting some confounding by indication for this drug class.

Even though we have seen a lower risk of HS for the MAO tranylcypromine, as well as for MAOs overall compared with amitriptyline/TCA use, these effects are most likely due to the selected population of MAO users. MAOs are contraindicated in patients with cardiovascular diseases in general, and specifically in patients with atrial hypertension. Additionally, dietary restrictions apply to avoid a critical increase in blood pressure that can occur under the use of MAOs when patients consume tyramine-containing foods (e.g. cheddar cheese) [34, 35].

The results presented for the individual agents seem to be at odds with the main analysis, but can be explained by the weight the individual agents have in the TCA and SSRI classes. Of 9136 cases and controls using TCAs at index day, 75 used amitriptylinoxide, 101 used clomipramine, 61 used imipramine, 140 used maprotiline, and 45 used nortriptyline compared with 2769 users of amitriptyline. In the 6009 users of SSRIs, 345 used fluoxetine, 70 used fluvoxamine and 671 used paroxetine. This indicates that the effect seen for SSRIs in the main analysis was mainly driven by citalopram (3551 patients) and escitalopram (547 patients). As confounding by indication or severity is potentially more problematic in analyses comparing individual agents, the differences between individual drugs with small numbers of users must be interpreted with caution.

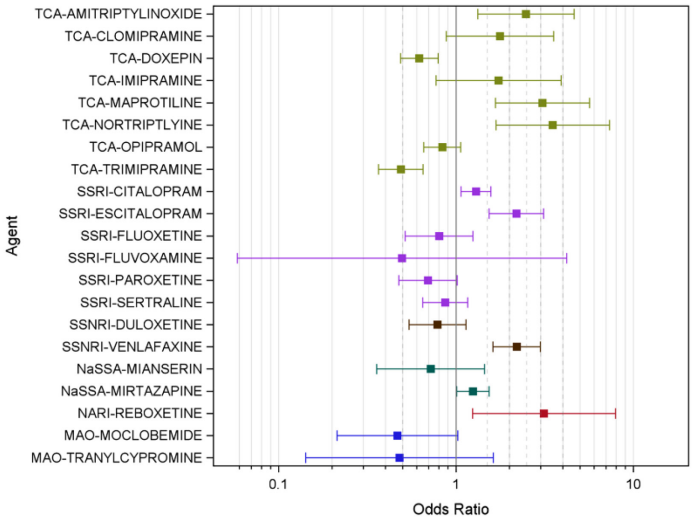

Fig. 1 Forest plot: risk of hemorrhagic stroke in current use of individual antidepressive agents compared with current use of amitriptyline (only individual drugs with at least one exposed case and control each are displayed). *TCA* tri- and tetracyclic antidepressant, *SSRI* selective serotonin reuptake inhibitor, *SSNRI* selective serotonin noradrenaline reuptake inhibitor, *NaSSA* noradrenergic and specific serotonergic antidepressant, *NARI* noradrenaline reuptake inhibitor, *MAO* monoamine oxidase inhibitor

The higher risks of HS for ADs inhibiting the reuptake of serotonin are to be expected as serotonin is an agent influencing the coagulation process, and the lack of serotonin, or at least a lower level of serotonin in the platelets, prolongs coagulation time [36]. Differences in the risk of HS or other bleeding events might be explained by differences in the strength of serotonin reuptake inhibition. However, even within the group of ADs with a high degree of serotonin reuptake inhibition (in this study, clomipramine, fluoxetine, paroxetine, sertraline and duloxetine), a high variability in the risk of bleeding events was observed [6]. Additionally, Renoux et al. [16] reported relatively small effects of 1.25 (1.01–1.54) for the group of strong versus weak inhibitors, and 1.13 (0.93–1.37) for intermediate versus weak inhibitors. These results might be partly explained by confounding by indication or severity, but at least indicate that the degree of serotonin reuptake inhibition does not seem to be the only factor explaining the increased risk of HS in the use of ADs.

Regarding exposure assessment, advantages of claims data are that patients had to receive the drug and pay the co-payment, that information on AD exposure is precise in terms of the dispensing date and drug product, and that recall bias can be ruled out. Contrariwise, information on the treatment pattern, actual dosage, and adherence to therapy is not available and the duration of supply had to be estimated; therefore, misclassification of exposure may have occurred. Furthermore, adding 150% of the supply to the DDDs to account for low dose and compliance, plus another 30 days to account for the long half-life of some of the ADs, might be an overestimation of exposed time. However, the observed risks of HS did not change in the sensitivity analyses with regard to the definition of supply and reflecting different assumptions on dose taken and overall adherence, indicating that it is not likely that misclassification of exposure had a considerable impact on the results.

Misclassification of the outcome was probably not an important issue in our study. In Germany, hospital main discharge diagnoses are considered to have high validity since they are based on all information relevant to diagnosis (including laboratory tests and imaging results) during the in-hospital stay and are subject to regular inspection. Nevertheless, we performed two sensitivity analyses excluding (1) patients without an imaging within 2 days of the index day, and (2) patients with a traumatic brain injury 30 days before the HS, which both yielded similar results as the main analysis, indicating that the effect of outcome misclassification on the results seems to be negligible. This is in line with a sensitivity analysis using imaging procedures in a previous GePaRD-based study on subarachnoid bleedings in antithrombotic users, where excluding patients without imaging procedures did not change the results either, supporting the validity of discharge diagnoses [37]. Please note that patients who were excluded in the sensitivity analyses might have had an imaging procedure that was not coded or performed outside of the time window of ± 2 days.

Even though adjustment for potentially confounding concomitant use of drugs such as antithrombotic drugs was performed, under-adjustment for these drugs might have occurred as concomitant use was defined as a supply that overlapped the index day. However, it might have been the case that this window was too strict.

Due to the nature of the database, information on lifestyle factors such as smoking, exercise, and diet, which are potential confounding factors for the occurrence of HS [38–40], were not included. Furthermore, as the GePaRD only holds information on medications reimbursed by the SHIs, information on the use of over-the-counter medication, such as nonsteroid anti-inflammatory drugs and acetylsalicylic acid, is missing. However, both lifestyle factors and use of over-the-counter medication are associated with several diagnoses and use of prescription drugs. By adjusting for a variety of covariates including these diagnoses and drugs, the results were also indirectly adjusted, at least in part, for the underlying lifestyle factors and use of over-the-counter medication.

A major strength of this study is its design, which addresses the methodological issues discussed by Douros et al. [17]. We nested our case–control analysis in a cohort of more than 700,000 incident users of ADs and thus avoided biases caused by the depletion of susceptibles and time-dependent hazard functions [23]. Furthermore, we chose an active comparator design and adjusted for many potential confounders and potential indications in the multivariable analysis to minimize confounding by indication. The large sample size of 4059 cases and 40,590 controls allowed us to investigate the potential effect modification by baseline bleeding risk and depression, and to assess the risk of HS for individual agents.

5 Conclusion

Our study shows that the use of medications inhibiting serotonin and/or noradrenaline reuptake increases the risk of HS in patients aged 65 years and older, and that the risk varies across individual ADs. HS remains a rare event, but physicians should carefully weigh benefits and risks when prescribing ADs to the elderly.

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Compliance with Ethical Standards

Conflicts of Interest Wiebke Schäfer, Bianca Kollhorst, and Tania Schink are employees of 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 post-authorization safety studies (PASS) requested by health authorities. The studies and the resulting publications are not influenced by the pharmaceutical industry. Christina Princk is currently an employee at the Governmental Institute of Public Health of Lower Saxony, Hanover, Germany, and has no conflicts of interest that are directly relevant to the content of this study.

Ethical Approval In Germany, the utilization of health insurance data for scientific research is regulated by the Code of Social Law. All involved SHIs, the German Federal (Social) Insurance, and the Senator for Science, Health and Consumer Protection in Bremen as their responsible authorities approved the use of the data for this study. Informed consent for studies based on the 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.

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Appendix D. P2

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ORIGINAL ARTICLE

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

1 | 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

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 exposure[14,15] 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 class[12] 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.

What is already known about this subject

- Antidepressant use has increased in recent decades. It is suspected that off-label use of antidepressants for indications showing a high prevalence among older adults (eg, insomnia) plays an important role in this regard.
- Studies on off-label prescribing of antidepressants in older patients are scarce and typically do not provide information for individual antidepressants.

What this study adds

- Based on more than 250 000 new users of antidepressants aged 65 years or older, this study suggests that more than 40% of all prescriptions are off-label.
- Although there was variation, the high prevalence of off-label prescribing 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.

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 drugs[17] 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 **opipramol** (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 Data 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 unspecific, 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 (F41.2) and a code for adjustment disorders (F43.2).

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

PHARMACOLOGY,[23] and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[24–30]

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, %)	7597 (2.9)	3736 (3.2)	3861 (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 Index[a]			
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, %)	9564 (3.6)	4107 (3.6)	5457 (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 physician[a]			
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)

[a]For 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.

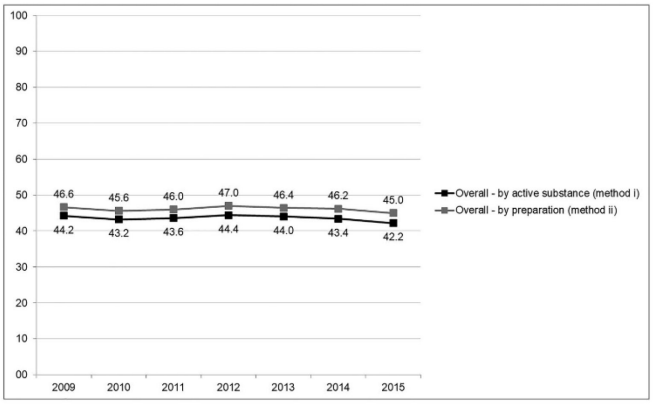

FIGURE 1 Proportion of off-label use of antidepressants among included persons stratified by year. Method (i) was used in the base-case analyses; it defines off-label use by the indications of the active substance. Method (ii) was used in the sensitivity analyses; it defines off-label use by the indications of the preparation

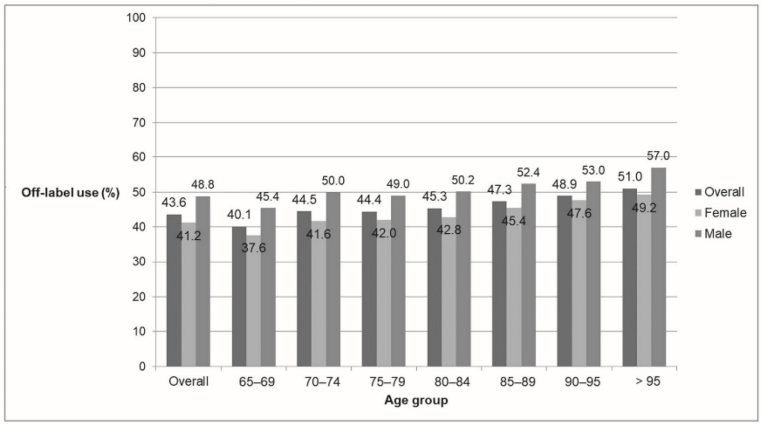

FIGURE 2 Proportion of off-label use of antidepressants according to age groups, stratified by sex. Method (i) was used in the base-case analyses; it defines off-label use by the indications of the active substance

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.[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.[13] Also Hanlon et al reported that 42% of US veterans without depression were prescribed one or more antidepressants.[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.[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,[13] while a survey from Sweden suggested a higher proportion of overtreatment among older women compared to older men.[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").[13] Hanlon et al[12] 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.[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 venlaflaxine, 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 venlaflaxine prescriptions was rather different between studies (20% of all antidepressant prescriptions in the study by Wong et al *vs* 2% in our study).[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[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.[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)[a]	Method (ii)[b]
Any[c] (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[d] (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 (483, 0.2%)	48.2% (43.8-52.7)	48.2% (43.8-52.7)
Imipramine (446, 0.2%)	59.9% (55.3-64.3)	54.5% (49.8-59.1)
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 homoeopathic (9889, 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)
Tranylcypromine (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 serotonergic antidepressant

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

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

[c]Additionally considering ICD-10-GM codes F41.2 and F43.2 for depression as indication.

[e]Amitriptylinoxide is included here.

[e]The proportion is 100% as the use of reboxetine is contraindicated above the age of 64.

[f]Agomelatine is contraindicated in patients aged 75 years or older.

TABLE 3 Distribution of factors[a] potentially associated with off-label prescribing in antidepressant users

	Total (n = 263 276)	Off-label users[b] (n = 114 923)	On-label users (n = 148 353)
Diagnoses (assessed in the year before cohort entry)			
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[c]	30 911 (11.7)	6563 (5.7)	24 348 (16.4)
Alcohol abuse	14 091 (5.4)	5554 (4.8)	8537 (5.8)
Diabetic polyneuropathy	9472 (3.6)	3692 (3.2)	5780 (3.9)
Drug abuse	7782 (3.0)	2504 (2.2)	5278 (3.6)
Bipolar disorders	1737 (0.7)	409 (0.4)	1328 (0.9)
Obsessive compulsive disorder	632 (0.2)	129 (0.1)	503 (0.3)
Diagnoses potentially associated with off-label prescription of antidepressants			
Diabetes[d]	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)	6864 (6.0)	7441 (5.0)
Parkinson's disease	11 751 (4.5)	4891 (4.3)	6860 (4.6)
Migraines	11 394 (4.3)	4150 (3.6)	7244 (4.9)
Fibromyalgia	3383 (1.3)	1096 (1.0)	2287 (1.5)
Schizophrenia	1569 (0.6)	646 (0.6)	923 (0.6)
Multiple sclerosis	994 (0.4)	363 (0.3)	631 (0.4)
Comorbidties (assessed in the year before cohort entry)[e]			
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	9831 (3.7)	3845 (3.3)	5986 (4.0)
Delirium	6630 (2.5)	3141 (2.7)	3489 (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)	9158 (8.0)	16 559 (11.2)
Hypnotics and sedative drugs	23 189 (8.8)	9593 (8.3)	13 596 (9.2)
Antiparkinsonian drugs	22 378 (8.5)	9455 (8.2)	12 923 (8.7)
Insulin	18 202 (6.9)	8329 (7.2)	9873 (6.7)
Atypical antipsychotics	17 041 (6.5)	6568 (5.7)	10 473 (7.1)
Antineoplastic drugs	14 148 (5.4)	6385 (5.6)	7763 (5.2)
Antidementive drugs	13 790 (5.2)	6667 (5.8)	7123 (4.8)
Lithium	1181 (0.4)	172 (0.1)	1009 (0.7)

TABLE 3 (Continued)

	Total (n = 263 276)	Off-label users[b] (n = 114 923)	On-label users (n = 148 353)
Special care (assessed in the year before cohort entry)			
Geriatric care	8402 (3.2)	3736 (3.3)	4666 (3.1)
Palliative care	6298 (2.4)	2919 (2.5)	3379 (2.3)

[a]The respective codes can be found in the Supporting Information Table S2. The prevalence of certain diagnosis may partly be overestimated given that an algorithm with high sensitivity was used to assess comorbidities. Of note, at the patient level there may be an overlap of diseases/disorders listed under different categories here (eg, Parkinson' disease and movement disorders).
[b]ICD-10-GM codes F41.2 and F43.2 were included for depression as indication.
[c]Assessed via ICD-10-GM codes F40 and F41, including all subcodes.
[d]Some antidepressants are indicated in the treatment of diabetic polyneuropathy.
[e]Diagnoses of diseases with a high prevalence in older adults or of diseases representing potential contraindications of antidepressants.

indication.[34–36] 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.[37–39] 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.[40,41] 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.[42] 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 hypertonia or arrhythmia, and the concomitant use of drugs metabolized via cytochrome P450 and its isoenzymes,[43] 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,[44] 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.[45] 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 minimises 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.[3,46] 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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COMPETING INTERESTS

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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Appendix E. P3

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Characterization of pregnancies exposed to St. John's wort and their outcomes: A claims data analysis

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ABSTRACT

Little is known about the utilization of St. John's wort (*Hypericum perforatum L.*) during pregnancy. In Germany, certain preparations of St. John's wort can be reimbursed by statutory health insurances, facilitating to investigate exposure to St. John's wort based on claims data. We therefore aimed to characterize pregnancies exposed to St. John's wort and to explore potential malformations in the babies. Using claims data from the German Pharmacoepidemiological Research Database (GePaRD), pregnancies exposed to St. John's wort during at least one trimester between 2006 and 2016 and the corresponding babies were identified. Exposure was identified via outpatient dispensations. Pregnancies were characterized regarding timing of exposure, use of other antidepressants, pregnancy outcomes and the occurrence of major malformations in the babies (not considering codes for musculoskeletal and other malformations due to low data quality in this regard). Out of 496 pregnancies with a dispensation of St. John's wort during pregnancy, 420 (85 %) had a dispensation during the first trimester. There was a dispensation of other antidepressants before pregnancy in 21 % (during pregnancy: 12 %). Eleven percent of pregnancies ended in non-live births. In 312 babies linked to 305 pregnancies, major malformations were coded in 18 babies (5.8 %), of which 17 were exposed in the first trimester. The crude relative risk of major malformations for babies exposed during the first vs. the second or third trimester only was 3.56 (0.48–26.17). Our results suggest that only in a minority of pregnancies, St. John's wort is used as an alternative to other antidepressants. Even though the relatively high rates of non-live births and major malformations after exposure to St. John's wort during the first trimester need to be interpreted with caution, the findings are striking and generate hypotheses that merit further investigation.

1. Introduction

Complementary and alternative or herbal medicines are used with increasing frequency [1–5]. Women, including pregnant ones, represent the majority of users of these medicines [1,3,5]. In contrast to many traditional herbal medicines with little to no evidence from trials [6–9], St. John's wort (*Hypericum perforatum L.*) has been studied in several clinical trials [10,11]. These studies demonstrated the effectiveness of St. John's wort in the treatment of mild depressive disorders, but there are also associated risks, e.g., due to drug-drug-interactions given that St. John's wort is a potent inducer of cytochrome P450 (CYP) 3A4 and P-glycoprotein [12–14].

In clinical trials investigating St. John's wort, pregnant women were – as is often the case – excluded. The European Medicines Agency has recommended not to use St. John's wort during pregnancy due to a lack of clinical data and equivocal results of animal studies [15], but these recommendations may not always be followed. Hence, observational studies are needed to get insights into utilization of St. John's wort among pregnant women and the outcomes of these pregnancies. However, such studies are rare [4,16–19]. There are only two surveys among pregnant women [17,18] and one case report of two pregnant women 16] which exclusively focused on St. John's wort. Other studies investigated utilization of herbs during pregnancy but did not report results specifically for St. John's wort [1,2,4,19]. Apart from this, there are

Abbreviations: ATC, Anatomical Therapeutic Chemical classification (version for Germany provided by the WIdO – AOK Research Institute); CI, confidence interval; CYP, cytochrome P450; GePaRD, German Pharmacoepidemiological Research Database; ICD-10-GM, International Classification of Diseases, 10th revision, German modification; OTC, over the counter; RR, relative risk.

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several studies investigating the safety of conventional antidepressants during pregnancy, but they did not include St. John's wort [20–25].

Even though large healthcare databases represent the main data source of drug utilization studies in pregnant women, they have not been used to investigate the utilization and safety of St. John's wort during pregnancy because St. John's wort is mostly sold over the counter (OTC) [26–30]. In Germany, St. John's wort is available as OTC drug but also – with the indication of moderate depressive disorders – as prescription medicine reimbursable by statutory health insurances [31]. This opens the possibility to conduct studies on women using St. John's wort during pregnancy based on German claims data.

In light of the information presented, we accordingly aimed to characterize pregnancies exposed to reimbursable St. John's wort preparations and to explore potential malformations in babies of these pregnancies using data from a large German claims database.

2. Material and methods

2.1. Data source

We used the German Pharmacoepidemiological Research Database (GePaRD) for this study. GePaRD 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 or later. In addition to demographic data, GePaRD contains information on dispensations of reimbursable prescription drugs as well as outpatient (i.e., from general practitioners and specialists) and inpatient services and diagnoses. Per data year, there is information on approximately 20 % of the general population and all geographical regions of Germany are represented [32,33].

In GePaRD, diagnosis codes are registered according to the International Classification of Diseases 10th revision, German modification (ICD-10-GM). For outpatient diagnoses, the additional coding of diagnostic certainty is mandatory in Germany. Drugs dispensed in the outpatient setting can be identified by the respective Anatomical Therapeutic Chemical (ATC) code. There is also information on the date of both prescription and dispensation. Regarding research on drug safety during pregnancy based on GePaRD, different algorithms to identify pregnancies including the date of the outcome and to classify pregnancy outcomes [34,35], to estimate the beginning of pregnancy [36], and to link mothers with their offspring [37] have been developed.

2.2. Study population and study design

Using the published algorithms [34–37], all pregnancies ending between 2006 and 2016 with at least one dispensation of a reimbursable preparation of St. John's wort between beginning and end of pregnancy were included. Accordingly, there had to be a defined end of pregnancy in the data, i.e., an outcome such as life birth or induced abortion. Censoring due to incomplete follow-up of the mother was thus not relevant. We excluded pregnancies in women with less than one year of database history before the beginning of pregnancy (i.e., continuous health insurance allowing a gap of 30 days between insurance periods). Corresponding to a cohort study, mothers were followed up to six months after the end of pregnancy, until end of insurance or death, whichever occurred first. If the pregnancy ended in a life birth and a child could be linked to its mother, the child was followed for 12 months, until end of insurance or death, whichever occurred first.

2.3. Variables

Baseline characteristics included the mother's age at the beginning of pregnancy and the number of outpatient physician visits, of hospitalizations, and of days hospitalized in the year before pregnancy as markers of healthcare utilization and overall health status. Additionally, the mother's highest educational degree was assessed. For each pregnancy, we determined the time until the first pregnancy-related examination, the duration of pregnancy and the outcome.

Drugs of interest included St. John's wort, other antidepressants, lithium, as well as antiepileptic drugs. Antiepileptic drugs were considered as several of these drugs are substrates of the cytochrome P450 pathways induced by St. John's wort, i.e., their concomitant use with St. John's wort can lead to decreased plasma concentration of these drugs. The latter also holds true for other medication such as antiviral drugs used in HIV therapy, but we did not put a special focus on these drugs as exposure to these drugs was expected to be very rare in the study population. For all dispensations, the specialty of the prescribing physician was assessed. Regarding diagnoses of the mother, the presence of diseases treated with antidepressants or lithium was assessed based on codes from the in- and outpatient setting.

The coding of malformations (ICD-10-GM Q00-Q99) was assessed in the in- and outpatient setting. We did not consider ICD-10-GM codes Q65-Q79.9 (musculoskeletal malformations) and Q80-Q89.9 (other malformations) as prior analysis of German claims data suggested wide and unspecific use of these codes. Codes used for the identification of diseases, medication, and pregnancy-related exams and the time-intervals during which they were assessed can be found in Appendix S1.

2.4. Plausibilization and classification of malformations

In children that could be linked to their mother, we first identified those with at least one of the selected codes for malformations. We then reviewed each of these profiles regarding the following criteria: 1) malformation was coded at least once in the inpatient setting, 2) malformation was coded repeatedly (especially relevant if coded only in the outpatient setting), 3) codes indicating a specific treatment or monitoring of the respective malformation were coded. We disregarded malformations that did not fulfill any of these criteria. We classified the remaining malformations as major and minor according to the EUROCAT [38] classification (minor malformations are, for example, tracheomalacia (Q32.0) or congenital malformations of eyelid (Q10.3)) and focused on major malformations in the subsequent analyses. Furthermore, we extracted information on whether the baby was born prematurely and whether a chromosomal defect (e.g., trisomy 21 or Turner syndrome) was coded.

2.5. Data analysis

We described all pregnancies regarding maternal characteristics, pregnancy duration and outcomes, and timing of dispensation of St. John's wort according to the following time windows: a) in the year before the beginning of the respective pregnancy, and b) during pregnancy, additionally sub-divided into i) between the beginning of pregnancy and the end of first trimester (defined as day 97 of pregnancy), ii) during the second trimester (defined as days 98–202 of pregnancy, and iii) during the third trimester (day 203 until the end of pregnancy). Use of antidepressants and antiepileptic drugs was assessed in the year before pregnancy and during pregnancy.

To explore the risk of malformations, we compared babies with exposure to St. John's wort during the first trimester to babies exposed to St. John's wort only in the second or third, or second and third trimester (exposure corresponds to the dispensation of St. John's wort to the mother in the respective time period). This approach of using babies also exposed to St. John's wort but not in the critical time window as controls is advantageous over totally unexposed controls as it likely ensures a higher comparability between the exposed and the non-exposed group. We disregarded malformations for which a possible other cause was coded (e.g., septum defects in children with premature birth or chromosomal defects such as trisomy 21 or Turner syndrome). We calculated crude relative risks (RRs) with 95 % confidence intervals (CIs) to assess the risk of any major malformations and also calculated

organ-specific risk estimates. In the organ-specific analysis, one child may have been counted twice if there were malformations in different organs. Children from twin pregnancies were considered independently in the analysis. All analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Characteristics of pregnancies exposed to St. John's wort and utilization patterns

Out of about 1.4 million pregnancies in GePaRD between 2006 and 2016 (see S1 Table), we identified 496 pregnancies with a dispensation of St. John's wort in at least one trimester (Table 1). Appendix S 2 provides information on the preparations of St. John's wort dispensed in this study. In about two thirds of pregnancies, the mother had a code for depression in the year before pregnancy and in one quarter, there was a code for anxiety, while in about one third neither a code for depression nor for anxiety was found. In 78 % of pregnancies, there was a dispensation of St. John's wort in the first trimester only, while 15 % of pregnancies were not exposed during the first trimester. The majority of prescriptions of St. John's wort (66 %) were issued by primary care physicians (Table 1; S2–4 Tables).

3.2. Concomitant utilization of other antidepressants and of antiepileptic drugs

Table 2 shows the dispensation of other medication before and during pregnancy (see also S5 Table). Dispensation of other antidepressants during pregnancy was seen in 58 pregnancies (12 %) and in 33 of these pregnancies (57 % / 7 % overall) antidepressants were also used before the beginning of pregnancy. In the year before the beginning of pregnancy, use of other antidepressants excluding St. John's wort was observed in 104 pregnancies (21 %). In 71 pregnancies (14 %), other antidepressants were exclusively used before the beginning of pregnancy. A switch from another antidepressant before the beginning of pregnancy to St. John's wort during pregnancy (i.e., no dispensation of St. John's wort before) was seen in 44 pregnancies (9 %). In eight pregnancies, there was a dispensation of an antiepileptic drug during pregnancy. There was an overlap between supply of St. John's wort and the antiepileptic drug and prescription of St. John's in four pregnancies including one overlap with carbamazepine (overlap was estimated based on the dispensation date; for details see Appendix S3).

3.3. Pregnancy outcomes

About 10 % of all pregnancies with a dispensation of St. John's wort ended before the beginning of the second trimester. The median duration of pregnancies was 277 days. Overall, 442 pregnancies (89 %) ended in live-births, i.e., there were 54 incomplete pregnancies. In all but one of these incomplete pregnancies there was a dispensation of St. John's wort in the first trimester (n = 54; see S4 Table).

3.4. Codes for malformations in the babies

Out of the 442 pregnancies ending in a live-birth, a mother-baby-linkage was possible for 305 pregnancies (69 %). Among these, there were seven twin pregnancies. In total, there were thus 312 babies for inclusion in the analyses regarding malformations (see S6a Table). Of these, 168 babies (54 %) were female. A total of 266 babies (85 %) were exposed to St. John's wort during the first trimester and 56 babies were exposed to St. John's wort only during the second or third trimester, but not during the first. After patient profile review and after excluding minor malformations (Fig. 1), 18 babies with malformations representing 6 % of all linked babies were included in the analysis regarding the risk of malformations. Of these, 8 babies (44 %) were female.

Table 1
Description of pregnancies exposed to St. John's wort regarding maternal characteristics, timing of exposure to St. John's wort and pregnancy-related characteristics.

	Total (N = 496; 100 %)
Characteristics of the mother[a]	
Age at the beginning of pregnancy	
Mean (SD)	32 (6)
Median (Q1–Q3)	32 (29–36)
< 18 years (n, %)	3 (0.6 %)
18–24 years (n, %)	51 (10.3 %)
25–29 years (n, %)	95 (19.2 %)
30–34 years (n, %)	164 (33.1 %)
35–39 years (n, %)	138 (27.8 %)
> 40 years (n, %)	45 (9.1 %)
Educational degree (n, %)	
Higher education (e.g., A-levels, high school, junior college)	170 (34.3 %)
Basic secondary degree /secondary degree (e.g., GCSE)	211 (42.5 %)
Degree unknown	115 (23.2 %)
Number of hospitalizations (n, %)[b]	
None	375 (75.6 %)
1–2	106 (21.4 %)
3–5	14 (2.8 %)
>5	1 (0.2 %)
Days hospitalized (n, %)[b]	
0–5 days	435 (87.7 %)
6–14 days	33 (6.7 %)
15–28 days	9 (1.8 %)
>28 days	19 (3.8 %)
Number of outpatient physician visits[b]	
Median (Q1–Q3)	19 (11–30)
None	5 (1.0 %)
1–5 (n, %)	43 (8.7 %)
6–10 (n, %)	72 (14.5 %)
> 11 (n, %)	376 (75.8 %)
Diagnoses before pregnancy (n, %)[b]	
Anxiety	123 (24.8 %)
Bipolar disorder	7 (1.4 %)
Depression	310 (62.5 %)
Epilepsy	9 (1.8 %)
Schizophrenia	2 (0.4 %)
Sleeping disorders	39 (7.9 %)
Severe infections	1 (0.2 %)
HIV	1 (0.2 %)
Multiple	133 (26.8 %)
None	158 (31.9 %)
Dispensation of St. John's wort	
Number with a dispensation before pregnancy (n, %)	165 (33.3 %)
Timing of dispensation of St. John's wort during pregnancy (n, %)	
1st trimester only	386 (77.8 %)
2nd trimester only	45 (9.1 %)
3rd trimester only	22 (4.4 %)
1st and 2nd trimester	17 (3.4 %)
2nd and 3rd trimester	9 (1.8 %)
1st and 3rd trimester	1 (0.2 %)
All trimesters	16 (3.2 %)
Specialty of physician prescribing St. John's wort in the first trimester (n, %)[c]	
Primary care	294 (70.0 %)
Gynecologist or obstetrician	3 (0.7 %)
Psychiatrist or psychotherapist	82 (19.5 %)
Other	41 (9.8 %)
Characteristics of pregnancies	
Duration of pregnancy (days)	
Mean (SD)	254 (63.2)
Median (Q1–Q3)	277 (267–282)
Min-Max	57–296
1–97 days (n, %)	49 (9.9 %)
98–230 days (n, %)	8 (1.6 %)
>230 days (n, %)	439 (88.5 %)
Type of pregnancy outcome (n, %)	
Live birth	442 (89.1 %)
Incomplete pregnancy	54 (10.9 %)
Still birth	5 (1.0 %)
Induced abortion	34 (6.9 %)

(continued on next page)

Table 1 (*continued*)

	Total (N = 496; 100 %)
Ectopic pregnancy	10 (2.0 %)
Spontaneous abortion	5 (1.0 %)

GCSE: General Certificate of Secondary Education.
[a] Women may be counted multiple times, according to their number of pregnancies exposed to St. John's wort.
[b] In the year before the beginning of pregnancy.
[c] Percentages refer to 420 pregnancies exposed during the first trimester. The group "others" includes physicians of other or unknown specialty, multiple prescriptions by physicians of different specialty.

Table 2
Drug use before and during pregnancy in pregnancies exposed to St. John's wort.

	Total (N = 496; 100 %)
Antidepressant use (n, %)[a]	
Before the beginning of pregnancy	104 (21.0 %)
Only before the beginning of pregnancy	71 (14.3 %)
During pregnancy, any time	58 (11.7 %)
During the first trimester	43 (8.7 %)
Only any time during pregnancy, but not before	25 (5.0 %)
Before and any time during pregnancy	33 (6.7 %)
Switching from antidepressant to St. John's wort	44 (8.9 %)
Use of antiepileptic drugs (n, %)[b]	
Antiepileptic drugs during pregnancy, any time	8 (1.6 %)
Antiepileptic drugs before pregnancy	9 (1.8 %)

[a] Excluding St. John's wort.
[b] Carbamazepine, clobazam, gabapentin, levetiracetam, pregabalin, valproic acid.

Exposure to St. John's wort occurred during the first trimester in 17 of these babies and only during the second or third trimester in one baby (see also S6b Table). Table 3 shows the location of the major malformations. The RR of major malformations in babies exposed to St. John's wort during the first trimester compared to those exposed during the second or third trimester only was 3.56 (0.48–26.17). For atrial septal defects, the RR for the first trimester was 2.64 (0.34–20.23) and for heart defects in general 3.16 (0.42–23.90). A sensitivity analysis excluding babies with an exposure to antidepressants or antiepileptic drugs during the first trimester did not lead to substantial changes in the risk ratio (RR of major malformations: 3.27 (0.44–24.06)). During the respective pregnancies, no other antidepressants were used, except for selective serotonin reuptake inhibitors (SSRIs) during the third trimester in two babies (see S7 Table). One of the babies exposed to St. John's during the first trimester was exposed to pregabalin during the first trimester. For Tables 1–3, additional results stratified by trimester of exposure as well as the distribution of comorbidities in the various exposure groups can be found in the supplement (S2–6b Table, S8 Table).

4. Discussion

In our study, we identified 496 pregnancies exposed to St. John's wort of which 78 % were exposed in the first trimester. Only in about 10 % of these pregnancies there was a switch from a conventional antidepressant before pregnancy to St. John's wort during pregnancy, suggesting that in our study population, St. John's wort played only a minor role as alternative treatment to avoid potential risks of other antidepressants during pregnancy. We observed the concomitant dispensation of St. John's wort and carbamazepine in one pregnancy illustrating that not all physicians are aware of the drug interactions related to St. John's wort which can reduce or eliminate the therapeutic effect of other drugs. Non-live births occurred in 11 % of included pregnancies. Out of the 442

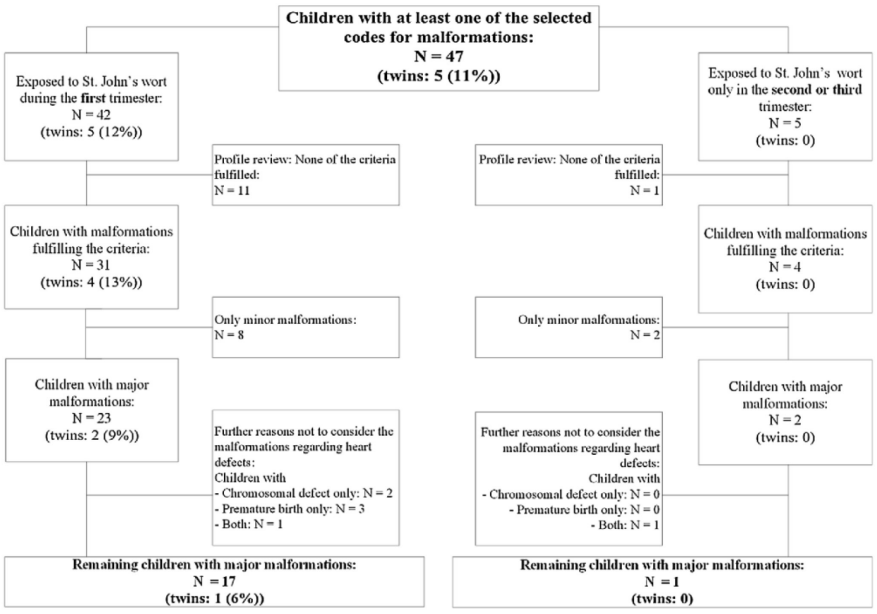

Fig. 1. Flow chart illustrating the in- and exclusion of babies with malformations.

Table 3
Location of major malformations in live-born babies exposed to St. John's wort during pregnancy.

	Number of babies
Total number of babies with major malformations considered in this study	18
Location of major malformation[a,b]	
Other defects of neural tube or brain (n, %)	3 (16.7 %)
Q02 – Microcephalus (n)	1
Q04.3 – Other reduction deformities of brain (n)	1
Q04.6 – Congenital cerebral cysts (n)	2
Cardio-vascular system (n, %)	13 (72.2 %)
Q20.4 – Double inlet ventricle (n)	1
Q21.0 – Ventricular septal defect (n)	3
Q21.1 – Atrial septal defect (n)	11
Q22.1 – Congenital pulmonary valve stenosis (n)	1
Q22.8 – Other congenital malformations of tricuspid valve (n)	1
Q23.0 – Congenital stenosis of aortic valve (n)	1
Q23.2 – Congenital mitral stenosis (n)	1
Q23.4 – Hypoplastic left heart syndrome (n)	1
Q24.4 – Congenital subaortic stenosis (n)	1
Q25.0 – Patent ductus arteriosus (n)	1
Q25.1 – Coarctation of aorta (n)	1
Q25.4 – Other congenital malformations of aorta (n)	1
Q25.6 – Stenosis of pulmonary artery (n)	2
Q28.8 – Other specified malformation of circulatory system (n)	1
Urinary tract (n, %)	4 (22.2 %)
Q60.0 – Renal angenesis, unilateral (n)	1
Q61.3 – Polycystic kidney, unspecified (n)	1
Q61.4 – Renal dysplasia (n)	1
Q61.8 – Other cystic kidney diseases (n)	1
Q61.9 – Cystic kidney disease, unspecified (n)	1
Q62.7 – Congenital vesico-uretero-renal reflux (n)	1
Q63.2 – Ectopic kidney (n)	2

[a] The table only lists groups if there was at least one baby with the respective malformation; babies were counted once per group and ICD-10-GM code, respectively, but may have been counted multiple times overall.
[b] Only ICD-10-GM codes used for diagnosis in at least one baby are presented. For a full list of codes sorted according to the groups see S2 Appendix.

pregnancies ending in a live-birth, a mother-baby linkage was possible in 305 pregnancies, leading to 312 babies in whom the occurrence of malformations could be assessed. Major malformations (excluding musculoskeletal and other malformations as explained in the methods section) were coded in 6 % of these babies, with defects of the heart being the most frequent malformation (72 %). In babies exposed to St. John's wort during the first trimester compared to the second or third trimester, there was a (statistically not significant) increased risk of major malformations overall (RR 3.56 (0.48–26.17)) as well as a (statistically not significant) increased risk of atrial septal defects (2.64; 0.34–20.23).

To our knowledge, this is the largest study on St. John's wort during pregnancy so far and the only study using claims data, i.e., a data source avoiding non-responder as well as recall bias. There are two studies to which we can compare our data. Moretti et al. identified 54 women who used St. John's wort during pregnancy in a prospective cohort of pregnant women contacting an information service on teratogens in Canada. They matched each of these women to one control with depression using conventional antidepressants, as well as to one control without depression and without exposure to antidepressants or known teratogens [18]. Kolding et al. identified 38 pregnancies exposed to St. John's wort before the 17th week of gestation from a birth cohort in Denmark and compared these to 90,128 pregnancies not exposed to St. John's wort during the first 17 weeks of gestation from the same cohort. In this study, live-born twins or sets of multiples were excluded from the analyses [17].

In our study, the mothers' mean age was similar to both other studies (about 32 years) while the mean duration of pregnancies in our study (254 days / 36 weeks) was shorter (Kolding et al.: 278 days, Moretti et al.: 39 weeks). Both in our and in the study by Moretti et al., most pregnancies were exposed to St. John's wort during the first trimester only and the majority of women had a diagnosis of depression and/or anxiety. Use of other antidepressants before or during pregnancy was not reported by Moretti et al. [18]. Compared to the study by Kolding et al., we found a higher prevalence of depression among users of St. John's wort (63 % vs. 5 %). Contrary to our study, other antidepressants were not used in pregnancies exposed to St. John's wort in the study by Kolding et al. [17].

Comparing the outcomes, we found that the proportion of pregnancies ending in non-live births in our study (11 %) was lower compared to the study by Moretti et al. (20 %) and higher compared to the study by Kolding et al. (3 %) [17,18]. These differences may be attributable to the method by which live and non-live births were identified. The algorithm to identify pregnancy outcomes in GePaRD underestimates the number of incomplete pregnancies among all pregnancies [34,35]. In the total number of pregnancies identified by this algorithm in GePaRD overall, however, the proportion of non-live births was 6 % [35], i.e., the proportion of non-live births of 11 % among users of St. John's wort seems to be relatively high compared to the proportion observed in GePaRD overall. In the study by Moretti et al., women were included at about 11 weeks of gestation (on average) and contacted again after the expected delivery date, i.e. this was a design facilitating a more complete assessment of pregnancy outcomes including non-live births [18]. The study by Kolding et al. was prone to underestimate the proportion of non-live births as it only included pregnant women in Denmark who, at their first visit to the general practitioner, wanted to carry their pregnancy to term [17].

Among 38 live-born children with first trimester exposure to St. John's wort, Moretti et al. observed a child with an obstructed ureter and a child with hypospadias [18]. Kolding et al. reported malformations in three children exposed to St. John's wort before the 17th gestational week including a bilateral hip dislocation, a heart septum defect, and hypospadias [17]. The anatomical locations (heart and urinary tract) of these malformations were thus similar to the findings in our study, but we did not find a case of hypospadias in GePaRD which may also be due to chance. As we did not consider musculoskeletal malformations (see methods section), hip dislocation could not be identified in our study. Even though the associations were not statistically significant in these studies nor in our study, the findings generated hypothesis that require further investigation, e.g., by pooled meta-analyses given that an increased risk of malformations due to St John's wort, particularly of the heart, does not seem implausible. Analogously to the mechanism of several antidepressants, St. John's wort is assumed to inhibit serotonin re-uptake [39–41]. Serotonin plays an important role as a signaling molecule in several aspects of the development of an embryo including the genesis of the heart. In children exposed to SSRIs during the first trimester, an increased risk of septal defects, and also specifically atrial septal defects was observed in several studies [25,42–48]. The same applies to selective serotonin norephedrine reuptake inhibitors (SSNRIs) [25,49]. The finding of a case of microcephalus was somewhat surprising as this is a rare malformation. According to EUROCAT data, the prevalence of microcephalus was 1 per 10,000 in 2018 [50].

4.1. Clinical relevance of findings and generalizability

The results of this study suggest that if St. John's wort is used during pregnancy, it is often used in the first trimester, and that utilization during the first trimester might be associated with an increased risk of malformations in the child. The relevance of this potential risk is further increased by the effect of St. John's wort on drug metabolism potentially reducing the effectiveness of oral contraceptives and thus increasing the likelihood of unintended pregnancies among women utilizing St. John's wort [51–54]. Physicians should therefore carefully balance the (uncertain) risks and benefits when prescribing St. John's wort to women

using contraceptives, women planning pregnancy or newly pregnant women. The same applies to pharmacists or employees of drug stores given that many preparations of St. John's wort are sold over the counter and also in form of food supplements. At the same time, when weighing risks and benefits of treatment with St. John's wort (or other antidepressants), it should be kept in mind that untreated depression in itself also bears a risk of harms [55–57].

4.2. Limitations

There are some factors limiting the results of the study as well as the comparison to previous studies on this topic. The pregnancies identified may not be representative of all pregnant women using St. John's wort during pregnancy given that only some preparations containing St. John's wort and only preparations with a higher dose are reimbursable while others are sold OTC, also as nutritional supplements. This also implies that the reported patterns of dispensations may underestimate actual exposure. Further, we only had information on the diagnoses coded in the women but not on the specific indication leading to the prescription. Another limitation is the underestimation of incomplete pregnancies, especially spontaneous abortions, based on the algorithm used in GePaRD. However, as the same algorithm identified a lower proportion of incomplete pregnancies in the total database [35], the proportion of incomplete pregnancies observed in pregnant women using St. John's is still remarkable. Given that our study was mainly designed to provide an overview on utilization of St. John's wort and a descriptive analysis of pregnancy outcomes, we only used a rough definition to classify exposure. In future studies specifically designed to assess risk of St. John's wort a more precise exposure definition would be required, taking into account the date of dispensations and the dispensed doses to estimate exposed time windows. Also, information on potential confounders such as alcohol consumption or smoking during pregnancy is limited in our database and was not considered in the analysis, which limits causal interpretation of our findings. The results of this study are further limited by the fact that the occurrence of musculoskeletal malformations (ICD-10-GM Q65-Q79.9) and other malformations (ICD-10-GM Q80-89.9) could not be investigated as the frequency of these codes in the database is far too high in GePaRD, indicating miscoding in this field. Regarding the relative risk, there is also statistical uncertainty due to the low sample size (particularly in the control group), illustrated by the large confidence interval around the point estimate of the risk ratio calculated here. Finally, children with codes of malformations in the claims data could not be linked to patient records or other data sources in order to obtain more detailed clinical information. To minimize this limitation, we conducted an in-depth case profile review taking into account all information on the malformations and their treatment or monitoring as far as available in the claims data.

4.3. Strengths

Our study also has several strengths. We used data from a large claims database, therefore avoiding non-responder and recall bias. Furthermore, the database contains all information on (reimbursable) health care services, in- and outpatient diagnosis codes, drugs dispensations as well as prescribing physicians. Unlike previous studies, this also allowed us, for example, to investigate concomitant use of potentially interacting drugs such as antiepileptic drugs. We were able to identify a sample size of pregnancies exposed to St. John's wort that was more than five times higher as compared to previous studies. With respect to the analysis on the risk of malformations, a strength of our study is the use of controls also exposed to St. John's wort but not in the critical time window rather than totally unexposed controls. This is expected to ensure a higher comparability between the exposed and the unexposed group with respect to confounding factors. Although the sample size was still low with respect to the power needed to estimate the risk associated with exposure to St. John's wort, our study provides important information for future meta-analyses which will be required to shed further light on this topic. An advantage of our database as compared to several other claims databases is the detailed information on the beginning of pregnancy, i.e., exposure during the first trimester can be ascertained with high accuracy [36]. Furthermore, we could also identify malformations not immediately diagnosed at birth given that in GePaRD—unlike in many other claims databases—children can be linked to their mother and then be followed up beyond birth.

5. Conclusion

In our study, St. John's wort was mainly utilized during the first trimester of pregnancy and rarely as an alternative to conventional antidepressants. We observed concomitant dispensation of St. John's wort and interacting medication suggesting that the awareness of drug interactions related to St. John's wort needs to be increased. Even though the relatively high rate of non-live births and the malformations of the heart observed in pregnancies exposed to St. John's during the first trimester need to be interpreted with caution, these findings generate hypotheses that merit further investigation.

Ethics approval and consent to participate

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 Office for Social Security and the Senator for Health, Women and Consumer Protection in Bremen as their responsible authorities approved the use of GePaRD data for this study. Informed consent for studies based on claims data is required by law unless obtaining consent appears unacceptable and would bias results, which was the case in this study. According to the Ethics Committee of the University of Bremen studies based on GePaRD are exempt from institutional review board review.

Availability of data and materials

In accordance with German data protection regulations, access to the data of the German Pharmacoepidemiological Research Database is granted only to employees of the Leibniz Institute for Prevention Research and Epidemiology – BIPS (BIPS) 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. Furthermore, as we are not the owners of the data we are not legally entitled to grant access to the data or to store data elsewhere, e.g., in a repository. This also relates to any kind of analysis datasets extracted from GePaRD.

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Authors' contributions

WS and UH conceptualised the research question. All authors contributed to the design of the study and the interpretation of the results. Data analysis was performed by WS. The manuscript was drafted by WS 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.

Conflict of Interest

WS, NW, TS and UH are working at an independent, non-profit 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 post-authorization safety studies (PASS) 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.

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Some results of the study were presented at the 36th International Conference on Pharmacoepidemiology and Therapeutic Risk Management (ICPE) in 2020 (online event ICPE All Access).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.reprotox.2021.04.005.

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Own contributions to the publications

As according to § 6 (2), sentences 2 and 4 of the Promotionsordnung for Dr. rer. nat at Faculty 11, University of Bremen, an overview on the candidate's own contribution to the publications with first authorship is provided in the table below.

Step	P1	P2	P3
Conceptualisation and research question	entirely	entirely	predominantly
Literature research	predominantly	entirely	entirely
Study plan	predominantly	entirely	entirely
Data collection[a]	--	--	--
Data analysis	entirely	predominantly	entirely
Discussion and interpretation	predominantly	predominantly	predominantly
Drafting of manuscript	predominantly	predominantly	predominantly
Revision	predominantly	predominantly	predominantly

[a] as all publications are based on pseudonymous secondary data, not collection of data was performed. Data management, (supervision of) programming of analysis datasets and statistical programming are included in "data analysis".
entirely: all steps performed independently in frequent exchange with colleagues; predominantly: the majority of steps performed independently;

Eidesstattliche Versicherung

Hiermit erkläre ich an Eides statt, dass ich die Arbeit ohne unerlaubte Hilfe angefertigt habe, keine anderen als die angegebenen Quellen und Hilfsmittel benutzt wurden sowie dass die den benutzten Werken wörtlich oder inhaltlich entnommene Stellen als solche kenntlich gemacht wurden.

Bremen, 22. April 2022