Leibniz Institute for Prevention Research and Epidemiology – BIPS GmbH

Final Scientific Report (Version 0.4)

Pharmacoepidemiological Safety Study of Neuroleptics and Antidepressants in the Area of Geriatric Psychiatrics (PhaSiNAg)

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Principal Investigators: Prof. Dr. Edeltraut Garbe, MSc Epidemiology and Biostatistics
garbe@bips.uni-bremen.de, +49-421-218-56862
Dr. Tania Schink, MPH
schink@bips.uni-bremen.de, +49-421-218-56865

Authors: Niklas Schmedt, M.A. Public Health
schmedt@bips.uni-bremen.de, +49-421-218-56868

Bianca Kollhorst, Dipl. Math.
kollhorst@bips.uni-bremen.de, +49-421-218-56980

Nils Fabian Gesing, Dipl. Math.
gesing@bips.uni-bremen.de, +49-421-218-56951

Address:
Leibniz Institute for Prevention Research and Epidemiology – BIPS GmbH
Achterstraße 30, 28359 Bremen, Germany
https://www.bips-institut.de/en/home.html

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Abbreviations

AD	Antidepressant
ADR	Adverse Drug Reaction
aHR	Adjusted hazard ratio
AOK	Allgemeine Ortskrankenkasse (German statutory health insurance provider)
AMI	Acute myocardial infarction
ASD	Absolute standardized differences ASD
ATC	Anatomical Therapeutic Chemical classification system
BIPS	Leibniz Institute for Prevention Research and Epidemiology – BIPS GmbH
BPSD	Behavioral and Psychological Symptoms of Dementia
CI	Confidence Interval
CPR	Central Pharmaceutical Reference database
CYP	Cytochrome P450
DAK	DAK-Gesundheit (German statutory health insurance provider)
DDD	Defined Daily Dose
DUS	Drug utilization study
GePaRD	German Pharmacoepidemiological Research Database
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiological Practice
GPS	Good Practice of Secondary Data Analysis
HF	Heart failure

HFR	Hip fracture
hkk	Handelskrankenkasse (German statutory health insurance provider)
ICD-10-GM	International Classification of Diseases 10th revision- German Modification
IRR	Incidence rate ratio
IS	Ischemic stroke
MAO	Monoamine oxidase inhibitor
NARI	Noradrenalin reuptake inhibitor
NL	Neuroleptic
PhaSiNAg	Pharmacoepidemiological Safety Study of Neuroleptics and Antidepressants in the Area of Geriatric Psychiatrics
PIM	Potentially inadequate medication
PN	Pneumonia
PY	Person Year
PZN	Pharmazentralnummer (Central pharmaceutical number)
SGB	Sozialgesetzbuch (German Social Security Statute Book)
SHI	Statutory health insurance provider
SSNRI	Selective serotonin noradrenalin reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tri- and tetracyclic antidepressant
TDEC	Target-drug-event-combination
TM	Total mortality
VA	Ventricular arrhythmia
VTE	Venous thromboembolism

1 Introduction

This final scientific report contains a brief summary of the objectives, methods, results and conclusions of all analyses conducted within the Pharmacoepidemiological Safety Study of Neuroleptics and Antidepressants in the Area of Geriatric Psychiatrics (PhaSiNAg). For better understanding, these are provided in the same structure as the reports were delivered during the project (1. Drug utilization study part1 – Population based cohort; 2. Drug utilization study part 2 - Neuroleptic and antidepressant user cohort, 3. Comparative safety studies and 4. Signal detection). Detailed information on all analyses is available in the specific study report.

For some modules, additional results were obtained for publication purposes that were not described in the previous study reports. The most important aspects are also shown and discussed briefly in the respective section of this report and the final results will be content of the respective publications.

2 Drug Utilization Study Part 1 – Population-based Cohort

Objectives

The main objective of this part of the drug utilization study (DUS) was to obtain detailed information on prescribing frequencies and drug use patterns of neuroleptics (NLs) and antidepressants (ADs) in persons aged 65 years and older.

Methods

Source of data for this study was the German Pharmacoepidemiological Research Database (GePaRD) which consists of claims data from four German statutory health insurance providers (SHI) covering over 17 million insurants throughout Germany. For this part of the DUS, a cohort design was applied to calculate the prevalence and incidence of NL and AD use for each year of the study period from 2005 to 2009 stratified by sex, age and selected comorbidities. Frequencies and percentages as well as mean and standard deviation, median and quartile 1 and 3, minimum and maximum were used to describe continuous and categorical variables, respectively. 95%-confidence intervals for prescription prevalence and cumulative incidences were calculated using the substitution method.

Results

In the yearly study cohorts the population ranged from approximately 1.86 million persons aged 65 years and older in 2005 to 2.37 million in 2009. Except for the cumulative incidence

over the study period, the population based measures of NL and AD use are only displayed for 2009 as this was the most recent data available in GePaRD at the time of analysis. In 2009, 2,373,710 persons were at least 65 years old and were therefore included in the cohort. The mean age was 73.2 years and 58.0% were female.

Overall, 5.5% received at least one NL and 12.1% at least one AD in 2009. In all age-groups, women were more likely to have received at least one NL or AD prescription compared to men. For both men and women, the prescription prevalence of NLs substantially increased with age. This pattern could also be observed for ADs in men, whereas the prescription prevalence of ADs in women decreased in the oldest age-group (=> 90 years). At least one conventional NL was prescribed to 3.7% of the study population, whereas 2.5% were treated with at least one atypical NL only. Less than one percent of the study population received both a conventional and atypical NL. Overall, 8.6% received at least one tri- and tetracyclic antidepressant (TCA) and 3.6% at least one selective serotonin reuptake inhibitor (SSRI). Monoamine oxidase (MAO) inhibitors, other ADs, selective serotonin noradrenalin reuptakes inhibitor (SSNRIs) and noradrenalin reuptake inhibitors (NARIs) had substantially lower overall prescription prevalences. Multiple ADs were prescribed to 1.6% of the study population. The prescription prevalence of NLs that were defined as potentially inadequate medication (PIM) according to the PRISCUS list was 0.6% in men and 1.0% in women. At least one PIM AD was much more frequently prescribed to women compared to men (6.7% vs. 2.9%).The most commonly prescribed NLs for both men and women was melperone followed by risperidone and promethazine. The ADs with the highest prescription prevalence were citalopram, amitriptyline, and mirtazapine. Nearly 40% of elderly patients diagnosed with dementia received at least one NL prescription whereas about 58% of persons with psychoses and 15% of persons with depression received respective treatment in 2009. In contrast, more than 40% of patients diagnosed with depression, 28.9% of those diagnosed with dementia and 36.5% of those with psychoses received at least one AD. The cumulative incidence of NL use increased from 2005 to 2006 and then steadily decreased until 2009. A similar development was found for PIM NLs. In comparison, the cumulative incidence of AD use slightly increased from 2005 to 2009, but decreased for PIM ADs.

Conclusion

In our study based on a large population of elderly persons in Germany, we found that NLs and especially ADs were prescribed to a large percentage of persons. This is generally in line with findings of previous studies from other European countries and Germany which primarily focused on patients living in nursing homes and/or with dementia. To our knowledge, our study is the first investigating the use of NLs and ADs in elderly persons in Germany on a

population level without restriction to specific indications or settings. In addition, our findings suggest that NLs and ADs are used for varying indications and that PIM NLs and ADs have often been used prior to the publication of the PRISCUS list. Warnings of public authorities between 2003 and 2005 regarding the use of NLs in elderly patients with dementia obviously did not have a major impact on the prescribing practice of physicians in routine care in Germany. Given the high prevalence of NL and AD use, it is important to study the comparative safety of frequently used NLs and ADs in elderly patients to prevent deaths and other severe adverse drug reactions and give evidence-based recommendations for NL and AD treatment options.

3 Drug Utilization Study Part 2 – Neuroleptic and Antidepressant User Cohort

3.1 *Summary*

Objectives

The main objective of this part of the DUS was to characterize NL and AD users aged 65 years or older with regard to drug use patterns (e.g. therapy discontinuation, switch to another drug, concurrent use of several drugs), and co-morbidity and co-medication to adequately plan the following safety studies.

Methods

For this part of the DUS, cohorts of NL (cohort 2) and AD users (cohort 3) were created to investigate drug use patterns as well as co-morbidity and co-medication. The study period started on January 1st, 2005 and ended on December 31st, 2009. Besides basic measures of NL and AD use (e.g. percentage of dispensed "Defined Daily Doses" (DDDs) of each individual NL and AD, percentage of dispensed DDDs of NLs or ADs administered orally or parenterally, estimated dose per dispensation of a drug), treatment episodes of NL and AD users were reconstructed and the following characteristics of NL and AD use were obtained: therapy discontinuation, switch to another drug, concurrent use of several drugs. Frequencies and percentages as well as mean and standard deviation, median and quartile 1 and 3, minimum and maximum were used to describe continuous and categorical variables, respectively.

Results

During the study period 302,998 patients aged 65 years or older received at least one NL. The mean age at cohort entry was 77.3 years and 68.6% were female. Approximately two-

third of patients entered the cohort with a conventional NL. Melperone was the drug that most often led to cohort entry (21.7%), followed by promethazine (16.4%), sulpiride (11.6%) and risperidone (9.9%). Overall, 231,173 patients (76.3%) were incident NL users and 68.4% received only one NL substance during time in cohort. Overlapping use of different NLs was rare.

Users treated with atypical index NLs were more likely to be diagnosed with psychosis, dementia, syncope or dizziness, and extrapyramidal and movement disorders. Patients with a conventional index NL far more often suffered from malignancies, cardiac arrhythmia, congestive heart failure and chronic pulmonary disease. Regarding co-medication, patients entering the cohort with an atypical NL were more likely to be treated with drugs against dementia or Parkinson's disease. In contrast, patients with a conventional index NL were more likely to be treated with anxiolytics and far more often received hypnotic or sedative drugs. Concurrent use of drugs sharing the same metabolic pathway as specific NLs was generally common.

The median treatment duration for any NL was 20 days. Treatment length was found to be shorter for atypical NLs (median: 14 days) and longer for those entering the cohort with both drug classes (median: 41 days). With approximately seven percent the proportion of patients with either switch to another NL or concurrent use of NLs during the first treatment episode after cohort entry was low. When therapy discontinuation was defined as a gap of more than 90 days between two treatment episodes, 28.2% of patients were found to have discontinued treatment. This proportion substantially decreased to 16.9% and 8.9% when allowing a gap of 182 or 365 days between two episodes, respectively. In total, 44.0% of incident NL users had only one treatment episode.

Overall, 490,114 persons aged 65 years or older received at least one AD. The mean age at cohort entry was 73.2 years and 72.7% were female. More than two-thirds of all patients entered the cohort with a TCA, followed by almost 20% receiving an SSRI. Amitriptyline was the drug that most often led to cohort entry (20.6%), followed by opipramol (16.3%), citalopram (12.3%) and doxepin (11.1%). Overall, 323,309 patients (66.0%) were incident AD users and 352,537 patients (71.9%) received only one AD substance during time in cohort. Overlapping exposure to different ADs was rare. For less than half of the patients entering cohort with a TCA a diagnosis of depression was found. Patients with a SSRI index AD were more likely to suffer from cerebrovascular disease, congestive heart failure and cardiac arrhythmia. Dementia was most often found in patients with NARI, followed by those entering cohort with a SSRI and least frequent in TCA users. Sleeping disorders were most frequent

among patients receiving multiple AD classes and those with a TCA. The proportion of co-prescribed opioids varied from 31.6% in those with a NARI index drug to over 40% in those receiving TCAs or SSRIs. Co-prescribing of anti-dementia drugs ranged from 4.9% in patients entering the cohort with a TCA to 18.5% in those receiving NARIs. Again, concurrent use of drugs sharing the same metabolic pathway as specific ADs was common.

Treatment length was found to be shortest for TCA users (median: 43 days) and longest for those entering the cohort with SSRIs or multiple AD classes (median: 251 days). When discontinuation was defined as a gap of more than 90 days between two treatment episodes, 24.7% of patients were found to have discontinued treatment. This proportion decreased to 17.6% and 10.2% when allowing a gap of 182 or 365 days between two episodes, respectively. Overall, with less than eight percent the proportion of patients with either switch to another AD or concurrent use of ADs during the first treatment episode after cohort entry was low and 59.6% of incident AD users had only one AD treatment episode during cohort time.

Conclusion

In this part of the drug utilization study, we obtained important information to adequately plan the following safety studies. We showed that new user designs are possible in the comparative safety studies due to a large percentage of incident NL and AD users. The observed drug use patterns in NL and AD users indicate that time dependent modeling of the exposure will not be mandatory, but sensitivity analyses with regard to the reconstruction of treatment episodes to prevent biased results due to exposure misclassification will be recommendable. Further confounding due to co-morbidity and co-medication and channeling bias might be present in the planned safety studies (especially for NLs) when comparing specific drug classes or individual drugs. Therefore confounders have to be carefully assessed in the primary analyses, and a secondary analysis should be considered that may control for unobserved confounding (e.g. high-dimensional propensity score or instrumental variable analyses). In addition, possible interactions with drugs sharing the same metabolic pathways as NLs and ADs via cytochrome P450 (CYP) isoenzymes might be present and should be addressed.

3.2 *Additional Analyses – Potential Indications and Treatment Duration*

For a publication on treatment patterns of NLs in elderly patients, more specific information on the prevalence of specific indications in the year prior to cohort entry were obtained from 298,847 new NL users between 2005 and 2011. The highest prevalence of dementia was observed in concurrent multiple users of conventional NLs and atypical NLs with 69.7%. Di-

agnoses of schizophrenia and bipolar disorders were rare except in concurrent multiple users of atypical NLs with 12.7% and 8.4%, respectively. Initiators of conventional NLs more often had a diagnosis of sleeping disorders, restlessness and agitation, as well as nausea and vomiting, and more often lived in nursing or residential care. In contrast, other psychoses and related symptoms, Parkinson's disease, other movement disorders, and dizziness or vertigo were more prevalent among atypical NL initiators. **Table 1** shows the prevalence of possible indications prior to cohort entry for the most frequently used individual NLs at cohort entry. These additional results reveal that NLs were used for a broad range of indications other than schizophrenia, bipolar disorders, and other psychoses in elderly patients in Germany, e.g., dementia, depression, pain or vertigo.

Table 1 Potential Indications of NL Users by Index NL

	Melperone N=70,022	Promethazine N=54,730	Fluspirilene N=28,018	Haloperidol N=22,958	Pipamperone N=15,475	Sulpiride N=32,841	Risperidone N=30,639	Quetiapine N=13,278	Olanzapine N=3,334	Tiapride N=2,208
Indications[2]										
Dementia	52.5%	14.4%	4.7%	29.3%	53.3%	8.2%	64.6%	45.4%	22.6%	26.2%
Schizophrenia and Related Disorders	0.5%	0.3%	0.4%	1.7%	0.7%	0.3%	3.4%	4.1%	10.3%	0.7%
Bipolar Disorders and Manic Episodes	0.7%	0.7%	0.7%	0.5%	1.2%	0.4%	1.3%	4.3%	12.7%	0.6%
Other Psychoses and Related Symptoms	5.3%	2.1%	2.3%	9.8%	6.2%	1.3%	17.7%	23.1%	27.6%	3.1%
Depression	31.0%	35.0%	56.1%	29.8%	38.5%	36.4%	34.0%	48.1%	65.4%	35.8%
Anxiety Disorders	6.7%	13.6%	16.3%	7.3%	9.6%	10.7%	7.1%	11.6%	17.9%	8.4%
Compulsive-Obsessive Disorders	0.2%	0.3%	0.3%	0.1%	0.2%	0.2%	0.4%	0.6%	1.4%	0.5%
Parkinson's Disease	6.8%	3.7%	1.6%	4.3%	6.9%	3.0%	6.0%	38.8%	6.7%	16.2%
Other Movement Disorders	4.6%	5.6%	5.2%	4.2%	5.0%	5.4%	3.7%	9.8%	6.2%	49.5%
Sleeping Disorders	20.3%	21.8%	17.1%	15.3%	22.7%	13.2%	13.4%	18.0%	17.3%	13.9%
Dizziness and Vertigo	12.6%	12.7%	14.5%	11.2%	12.6%	59.8%	11.9%	12.2%	10.6%	14.3%
Restlessness and Agitation	11.0%	8.2%	4.6%	6.6%	10.5%	1.7%	8.1%	5.9%	4.6%	3.7%
Nausea and Vomiting	6.2%	6.1%	3.8%	17.3%	5.5%	5.1%	4.0%	4.4%	4.5%	4.1%
Pain	33.6%	42.4%	48.5%	49.2%	35.1%	46.8%	30.8%	36.8%	34.7%	35.6%
Nursing or Residential Care	14.9%	5.1%	0.7%	10.4%	12.8%	1.3%	14.2%	8.6%	5.7%	8.9%

Q1/Q3 = First/Third Quartile,[1] assessed within 365 days prior to cohort entry, [2] assessed within 182 days prior to and at cohort entry, [3] assessed at cohort entry

As a further additional analysis, we calculated the treatment duration (persistence) of the index NL stratified by drug class adding 0%, 50%, 100%, 200%, and 300% of the prescribed DDD to each NL dispensation for the construction of treatment episodes and displayed it in boxplots to prove the consistency of our definitions in the primary analysis which added 150% of the prescribed DDD. The overall median persistence continuously increased from eight days when adding 0% to 31 days when adding 300% to each NL dispensation. This was observed for initiators of both conventional and atypical NLs (**Figure 1**). Longer treatment duration with higher percentages added to the DDD supply may be related to continuous use at lower dosage or frequent "as-needed" treatment of the same drug highlighting the importance to conduct sensitivity analyses with regard to the definition of current treatment in comparative safety study of NLs.

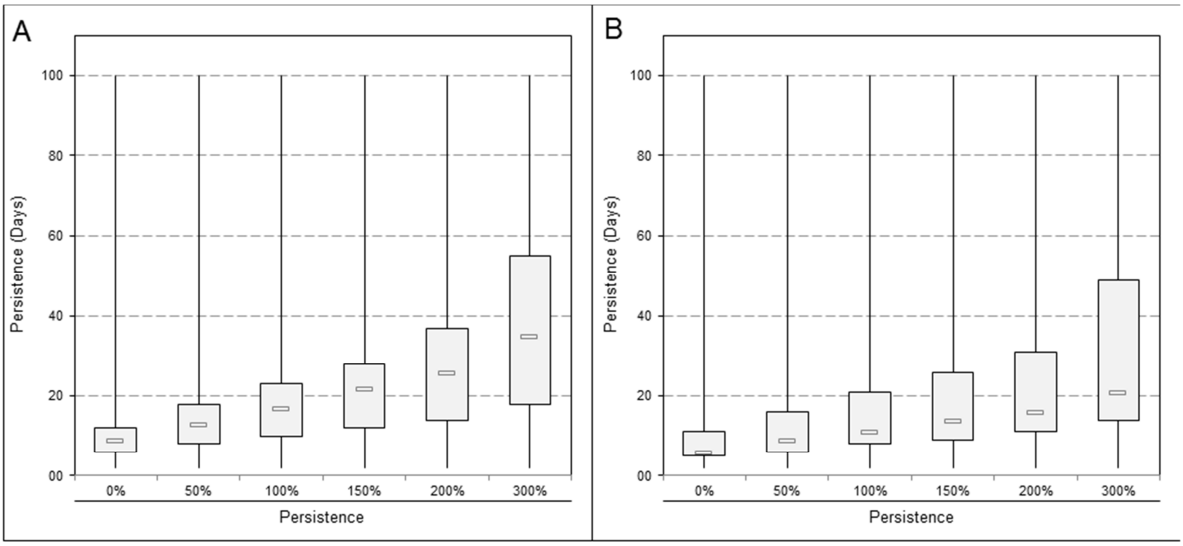

Figure 1 Boxplot of Median Treatment Duration with the Index Conventional NL (A) and Atypical NL (B) with Varying Percentages added to the DDD Supply

4 Comparative Safety Study

4.1 *Summary*

Objectives

The objective of the comparative safety study was to estimate the risk of heart failure (HF), acute myocardial infarction (AMI), ventricular arrhythmia (VA), ischemic stroke (IS), hip fracture (HFR) and all-cause mortality for users of NLs and ADs aged 65 years and older and to compare these risks between individual drugs and drug classes. For NL users, the outcomes pneumonia (PN) and venous thromboembolism (VTE) were also investigated.

Methods

A retrospective cohort design was used to estimate the risk of the outcomes under study for incident users of NLs and ADs aged at least 65 years and to compare these between individual NLs and ADs and drug classes based on the German Pharmacoepidemiological Research Database (GePaRD). The study period started on January 1st, 2005 and ended on December 31st, 2011 (depending on the availability of data from the individual statutory health insurance (SHI) providers). Two cohorts were created including incident NL or AD users aged 65 years or older, respectively. In the primary analysis, NL and AD users were analyzed based on the initial treatment assignment and were followed to the end of insurance, the occurrence of the outcome, 180 days after cohort entry or dispensation of a NL (the latter only in the AD user cohort). In a secondary analysis, NL and AD users were censored, if they discontinued treatment with the index drug or switched therapy. The occurrence of each of the outcomes was defined using the first main discharge diagnosis after cohort entry. Potential interactions with drugs sharing the same metabolic pathways via cytochrome P450 (CYP) isoenzymes according to the "Flockhart list" were investigated for risperidone and citalopram for all outcomes. Therefore, users of risperidone and citalopram using an inhibitor of one of the main metabolizing CYP at cohort entry (CYP2D6 and CYP2C19, respectively) were compared to those without respective co-medication (reference group). To control for potential differences in the characteristics of patients who were prescribed different drug classes, propensity-score (PS) adjusted analyses were also conducted. Furthermore, the primary analysis was repeated for all outcomes comparing users of PIM NLs and ADs with users of non-PIM NLs and ADs, respectively. The incident NL and AD user cohorts were described with respect to the baseline characteristics sex, age at cohort entry, follow-up time as well as co-morbidity and co-medication. Crude incidence rates for each outcome per 1,000 person-years were calculated for users of NL and AD drug classes and individual drugs, stratified by sex and age-group. Cox models were used to estimate the adjusted hazard ratio (aHR) for each outcome in the NL and AD drug classes and for frequently used individual drugs using the time until an event or censoring as time scale.

Results

During the study period 309,273 persons aged 65 years or older were identified as incident users of NLs. The median age at cohort entry was 78 years and 68.0% were female. More than two-thirds of both men and women entered the cohort with a conventional NL. Melp-

erone (23.2%) was the drug that most often led to cohort entry (i.e. the index drug), followed by promethazine (18.2%), sulpiride (11.0%) and risperidone (10.3%).

Compared to atypical NLs the use of conventional NLs yielded an elevated risk for HF in the primary analysis (aHR 1.15; 95% CI: 1.08-1.23). A similar result was found after PS-adjustment, whereas a higher aHR was found in the secondary analysis. Comparing individual NLs to risperidone, lower risks were found for tiapride, sulpiride, fluspirilene and quetiapine, whereas for amisulpride an increased risk of HF was observed. Use of conventional NLs did not increase the risk of AMI compared to atypical NLs in the primary analysis (aHR: 1.04; 95% CI 0.93-1.16). Comparing single NLs to risperidone revealed the lowest risks for fluspirilene and sulpiride. For VA, the risk did not differ between conventional and atypical NLs in the primary analyses (aHR: 1.07; 95% CI 0.82-1.41). The secondary analysis yielded a substantially higher aHR estimate, where CIs included the one. Among individual NLs, significantly decreased risks for VA were found for fluspirilene, levomepromazine and sulpiride compared to risperidone. The risk for IS did not differ between conventional and atypical NLs (aHR: 0.98; 95% CI: 0.91-1.05). On a substance level, a significantly decreased risk for IS was found for fluspirilene and promethazine compared to risperidone. With regard to HFR, use of conventional NLs slightly increased the risk compared to atypical NLs (aHR: 1.10; 95% CI: 1.02-1.18). The same result was found in the PS-adjusted analysis, whereas no statistically significant risk was observed in the secondary analysis. On a substance basis significantly decreased risks for HFR were found for fluspirilene, sulpiride and promethazine compared to risperidone. In contrast, significantly elevated risks for HFR were observed for haloperidol, quetiapine, pipamperone and melperone. No difference in the risk for PN was observed for conventional NLs and atypical NLs (aHR: 1.02; 95% CI: 0.96-1.09). Compared to risperidone, all NLs except haloperidol, zuclopenthixol, clozapine, amisulpride and aripriprazole decreased the risk of PN significantly. Use of conventional NLs slightly decreased the risk of VTE compared to atypical NLs (aHR: 0.91; 95% CI: 0.82-1.02) without reaching statistical significance. On a substance basis, the lowest risks compared to risperidone were found for sulpiride and fluspirilene, but were also observed for melperone, quetiapine, prothipendyl and promethazine. Use of conventional NLs substantially increased the risk of death compared to treatment with atypical NLs (aHR; 1.53; 95% CI: 1.49-1.57). Compared to the primary analysis, a slightly lower aHR was observed after PS-adjustment, whereas an additional censoring by end or switch of treatment yielded a higher estimate. On a substance basis, levomepromazine, haloperidol, zuclopenthixol and melperone were associated with a higher risk of death compared to risperidone. For all other NLs, except pipamperone, amisulpride and aripiprazole, a lower risk compared to risperidone was found. Excluding patients with a history of cancer yielded a lower aHR (1.29; 95% CI: 1.25-1.33) compared to the

overall cohort. In the adjusted exploratory analyses, risperidone users with CYP2D6 inhibitor co-medication at cohort entry revealed a slightly increased risk of death compared to those without such co-medication (aHR: 1.17; 95% CI: 1.06-1.28). The comparison of PIM and non-PIM NLs according to the PRISCUS-list showed a higher risk of HFR, PN and VTE and a 75% elevated risk of death for PIM compared to non-PIM users.

During the study period 439,317 persons aged 65 years or older received an incident AD dispensation. The median age at cohort entry was 72 years and 71.8% were female. More than two-thirds of patients entered the cohort with a TCA, followed by almost 20% receiving a SSRI. Amitriptyline was the drug that most often led to cohort entry (21.3%), followed by opipramol (17.3%), citalopram (14.3%) and doxepin (9.5%). Compared to TCAs only SSRIs showed a slightly elevated risk of HF (1.08; CI: 1.01-1.16) in the primary and the PS-adjusted analysis. In contrast, the secondary analysis showed no significant differences for any of the classes compared to TCAs. On a substance basis, slightly decreased risks of HF were observed for hypericum, trimipramine and amitriptyline compared to citalopram. For AMI, decreased risks without reaching statistical significance were observed for SSRIs (aHR: 0.93; 95% CI: 0.83-1.05), MAO inhibitors (0.72; 0.27-1.93) and other ADs (0.87; 0.66-1.15) in comparison to TCAs. Comparing single ADs to citalopram revealed a significantly decreased risk of AMI for escitalopram. With regard to VA, all AD classes showed slightly elevated risks compared to TCAs which however did not reach statistical significance. On a substance basis no statistically significant effects were found for VA when compared to citalopram. SSRIs showed a higher risk of IS compared to TCAs (1.17; 1.08-1.27), whereas use of other ADs was associated with a decreased risk (0.70; 0.56-0.89). On a substance level decreased risks of IS compared to citalopram were observed for several ADs including opipramol, trimipramine and hypericum. Compared to TCAs, both SSRIs and SSNRIs showed a considerably higher risk for HFR (1.58; 1.45-1.71 and 1.43; 1.17-1.76, respectively). In contrast to that, use of other ADs was associated with a decreased risk of HFR (0.67; 0.51-0.87). Among individual ADs, several substances showed a decreased risk for HFR compared to citalopram. The lowest risks were observed for opipramol, trimipramine and doxepin. With regard to mortality, SSRIs and MAO inhibitors showed an increased risk (1.18; 1.14-1.22 and 1.27; 1.02-1.59, respectively) compared to TCAs. On the contrary, decreased risks were observed for SSNRIs (0.78; 0.72-0.86) and other ADs (0.63; 0.57-0.71). On a substance basis, several drugs revealed a decreased risk of death compared to citalopram including opipramol, trimipramine, duloxetine and hypericum. In the adjusted exploratory analyses, users of citalopram with CYP2C19 inhibitor co-medication at cohort entry yielded a statistically significant increased risk of death compared to those without such co-medication (1.28; 1.20-1.36).

The comparison of PIM and non-PIM ADs showed slightly decreased risks for HF and VA, whereas a slightly increased risk for PIM ADs was only found for mortality.

Conclusion

Our study adds important information on the comparative safety of NL and AD drug classes and individual drugs, since most previous studies did not have the statistical power to adequately investigate these topics and did not include substances that are used almost exclusively in Germany.

Overall, our study suggests that atypical NLs have a better safety profile compared to conventional NLs. Although we did not find differences for AMI, IS, PN and VTE, our study suggests that users of conventional NLs might be at higher risk for HF and HFR resulting in a higher risk of death compared to atypical NLs. For VA, a higher risk for conventional NLs is also suspected, but requires further investigation. The same applies for IS in patients with dementia. On a substance level it is notable that for many outcomes, no differential risks were found for NLs that are frequently used in elderly patients, especially in dementia. With regard to the most important outcome all-cause mortality, haloperidol and levomepromazine were associated with a substantially increased risk of death compared to risperidone and should therefore not be used in elderly patients except in palliative care. Surprisingly, risperidone might be associated with a higher risk of death compared to many other NLs, although it is the only NL explicitly indicated to treat behavioral and psychological symptoms of dementia (BPSD). If no substantial risk factors for falls and fractures exist, quetiapine might be an adequate treatment alternative. However, due to the broad range of NL indications and different risk factor profiles, further analyses that address residual and unmeasured confounding (e.g. instrumental variables, high-dimensional propensity scores) are planned for publication to consolidate our findings. For instance, strong beneficial effects observed for the NLs fluspirilene, sulpiride and partly for promethazine and tiapride should be interpreted cautiously due to possible confounding by indication. Our study also showed that the PRISCUS list has a clinical relevance for NLs, since PIM NLs were associated with a higher risk of HFR, PN, VTE and death. Although treatment choice should take into account individual patient characteristics, the use of PIM NLs should be avoided whenever possible. The same applies for concomitant use of drugs that share the same metabolic pathways via CYPs, since such co-medication seems to be associated with a higher risk of death.

Regarding AD use, we found no evidence that use of SSRIs was safer in elderly persons compared to TCAs. Overall, significantly increased risks of HFR and – to a lesser extent – of mortality and IS were observed for SSRIs. Although the lack of dosing information has to be

considered as a major drawback, the results in the subgroups of patients with depression and opioid co-medication indicate elevated risks for SSRIs also in more homogenous populations. On a substance level, citalopram seemed to be associated with comparatively high risks for most of the outcomes, although it was chosen as comparator due to its broad range of indications, common use and non-PIM status. However, the ADs which overall showed the most beneficial effects in our study, i.e. opipramol and hypericum, cannot be generally considered an alternative to the ADs associated with higher risks due to their restrictive indications. Overall, a clear association between the outcomes and PIM ADs was only found in the mortality analysis which yielded a comparatively high risk for the PIM amitriptyline. Surprisingly an increased risk of hip fractures associated with PIM ADs could not be observed in our study, although many ADs were considered as PIM due to their possibly increased risk of falls and hip fractures.

In conclusion, this study provides a comprehensive overview on the risks of several important outcomes associated with the use of specific NL and AD drug classes and individual drugs in routine clinical practice. Stratifying by potential indications for use also allowed us to examine these risks in different subgroups of patients. As discussed above, further analyses and a more detailed discussion are planned for specific outcomes with heterogeneous results to consolidate our findings and for the purpose of publication.

4.2 *Additional Analyses*

4.2.1 Neuroleptics and All-Cause Mortality

For a publication of the comparative safety of NLs regarding the outcome all-cause mortality, the original analyses were repeated for individual NLs after exclusion of patients with a history of cancer. Many NLs are used as sedative or anti-emetic in palliative care which might have led to overestimation of the risk estimates for some NLs in the original analyses, especially for haloperidol and levomepromazine. In addition, the maximum follow-up was reduced from 180 days to 90 days as primary analysis considering the short treatment duration for most NL users. **Figure 2** displays the results obtained from these different analysis strategies for selected NLs compared to risperidone. The adjusted hazard ratio of mortality for haloperidol and levomepromazine was substantially lower after the exclusion of cancer patients in the analysis with a maximum follow-up of 182 days compared to the original analysis, but still significantly increased. These findings illustrate that including cancer patients in the original analyses biased the results leading to an overestimation of the mortality risk for haloperidol and levomepromazine. However, the observed higher risk for both drugs with a maximum

follow-up of 90 days is in line with our previous results indicating a higher risk of death for these drugs shortly after initiation of therapy compared to risperidone. In contrast, the risk estimates for melperone, olanzapine and quetiapine were similar across all analyses. While melperone might be associated with a slightly higher risk of death compared to risperidone, it might be substantially lower for users of quetiapine and olanzapine. For publication, it is further planned to apply high-dimensional propensity score methods to explore the impact of unmeasured confounding and to consolidate our findings.

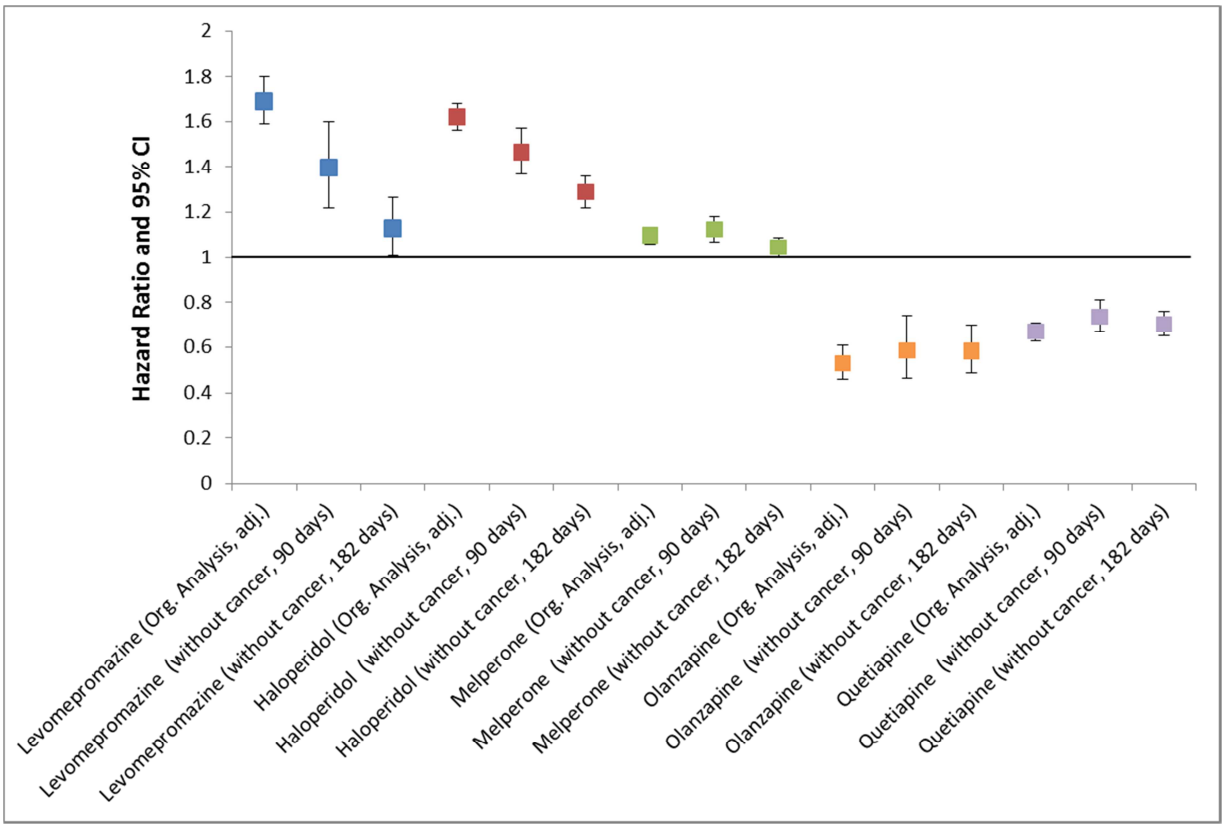

Figure 2 Comparison of adjusted hazard ratios of mortality before and after the exclusion of patients with cancer for selected neuroleptics compared to risperidone

4.2.2 Antidepressants and All-Cause Mortality – Instrumental Variable Analysis

Objective

For a publication of the all-cause mortality among antidepressant users, the validity of the physician's preference as an instrumental variable (IV) has been investigated. Using an IV instead of the actual treatment is equivalent to pseudo-randomizing the patients to alternative treatments. However, IV analysis can reduce bias in effect estimates due to unmeasured confounding, only if a valid instrument can be identified. An observable variable is a valid

instrument provided that all three following assumptions are met. First, the IV is associated with the treatment. Second, the IV is independent of unobserved confounders and third, conditionally on unmeasured confounders and treatment, the IV and the outcome are independent, implying that the IV association with the outcome is fully mediated by the observed treatment.

Methods

For this analysis, only the sub-cohort of TCA and SSRI users were considered. For the actual treatment, patients were classified as users of either TCA or SSRI, depending on the first prescription, at cohort entry. The binary instrument (PP1) was an indicator variable, assigned the value of 1 or 0 if the prescription written to the most recent patient by the same physician was for a SSRI or for a TCA, respectively. The continuous instrument (PP2) was defined as the proportion of all previous patients of the same physician who were prescribed an SSRI in the study period. To investigate whether the first IV assumption is satisfied, three measures of the strength of the association between the IV and the actual treatment were calculated, separately for each of the two instruments. The three measures were: the partial F-statistic for the adjusted IV effect, the squared partial correlation r2, and the estimated effect of the IV on the probability of treatment, quantified as the adjusted difference in prevalence (per 100 patients). Neither the second nor the third IV assumption can be empirically verified, but the plausibility of both can be explored. To check whether the second assumption may be considered as being valid, the balance of measured covariables across levels of the treatment and levels of the instruments were assessed using a linear model as large imbalances in measured covariables may signal potential confounding by unmeasured covariables. For this purpose, the continuous instrument PP2 was dichotomized using the first and the third quartiles as cut-points. Furthermore, estimates were adjusted for the year of AD prescription and standard errors were calculated robustly accounting for clustering by physician. As the third assumption cannot be explored based on the data, we examined the association between the IVs and benzodiazepines prescribed at the same day as the AD prescription using a logistic model, adjusted for age, sex and year of the index AD prescription. A violation of the third assumption would occur if the physician's AD preference is associated with the concomitant prescribing of a potentially hazardous medication in the elderly. To account for the clustering by physician, the parameters and standard errors were estimated using a robust generalized estimating equation approach and a working variance-covariance matrix with an exchangeable structure.

Results

The sub-cohort consisted of 398,304 TCA and SSRI users. 593 patients had to be excluded due to a missing identifier of the physician. Since the prescription of the first patient of each physician was used to assess his or her preference, the first patient of each physician was excluded (67,386 patients). This resulted in the final sample size for the IV cohort of 330,325 patients. The overall proportion of patients in the sub-cohort with a SSRI as the first AD prescription was 22.6% (IV cohort: 22.7%).

Figure 3 Balance of observed covariables for treatment and instrumental variable PP1

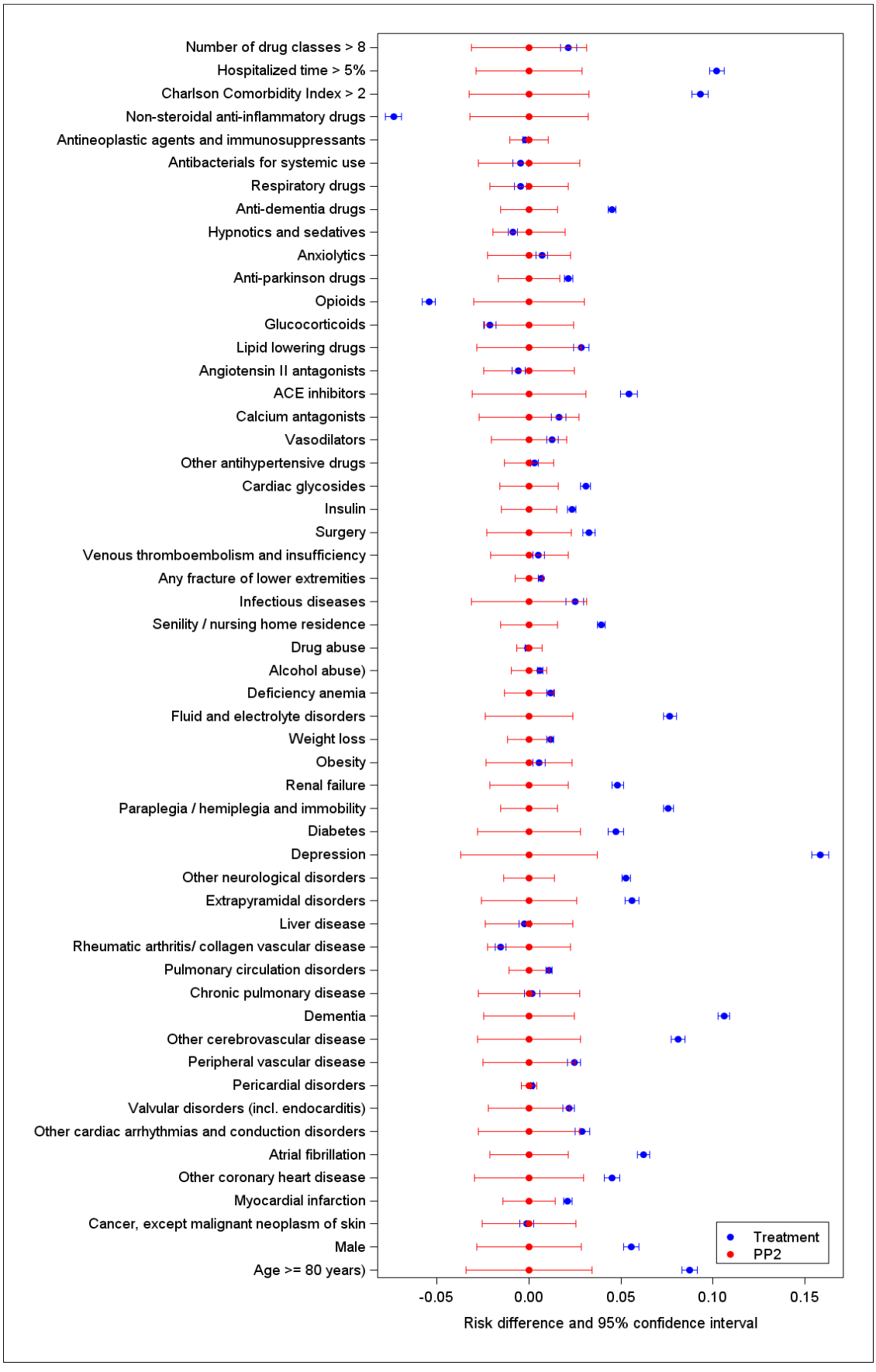

Figure 4 Balance of observed covariables for treatment and instrumental variable PP2

Table 2 compares the values of the three statistics used to assess the instruments´ strength. In general, the continuous physician's preference (PP2) was a stronger predictor of the actual treatment than the binary instrument (PP1), according to both the partial r2 and the F-statistics. Both instruments met the Staiger and Stock criterion of an F-statistic greater than 10, but their high values reflected the very large sample sizes. In contrast, the low values of the partial r2 indicated that the instruments explained only a very small proportion of the variance in the actual treatment assignments. The difference in prevalence for the binary instrument indicated that if the physician previously prescribed a SSRI, the next patient would be about 11% more likely to also be prescribed a SSRI. However, the effect of the continuous instrument indicated that the next patient would be about 34% more likely to be prescribed a SSRI if the proportion of all previous patients of the same physician, who got SSRIs, increased 100%.

Table 2 Strength of the association of the actual treatment with the instrumental variables

Instrument	Partial F-statistic	Partial r2	Difference in prevalence of SSRI per 100 patients (95% CI)
PP1	3,995	0.012	10.6 (10.2 - 10.9)
PP2	7,370	0.017	33.7 (32.9 - 34.4)

The two actual treatment groups were highly imbalanced for most of the covariables. Both instruments improved the balance in all covariables (**Figure 3 and Figure 4**). The improvement of balance was comparable for both IVs.

Regarding the association of a potential hazardous co-prescription of a benzodiazepine with the instruments, the estimate implies the odds of the physician to co-prescribe a benzodiazepine to his/her current patient is 19% higher if the physician prescribed a SSRI, compared to a TCA, to the previous patient (odds ratio (95% CI): 1.19 (1.14 - 1.25). Using the IV based on the proportion of all previous patients, physicians were more likely co-prescribe a benzodiazepine (odds ratio (95% CI): 1.66 (1.49 - 1.84).

Conclusion

Both instruments meet the assumptions for a potential instrumental variable for the patients' actual prescriptions of SSRI vs. TCA and, thus, may reduce the impact of unmeasured con-

founding. We found that both instruments improved the balance in the distribution of the observed confounders and, hence, may be also expected to be less associated with unobserved confounders. However, the instrument based on the previous prescription is very weak and the instrument based on the proportion of previous prescriptions is only moderately strong, so that the resulting variance inflation will make it difficult to derive robust conclusions about the treatment effect. In addition, the violation of the third assumption would further introduce bias in the estimates. Due to the reasons mentioned above, this analysis will not be used in a publication.

5 Signal Detection

Objectives

The objective of this part of the Pharmacoepidemiological Safety Study of Neuroleptics and Antidepressants in the Area of Geriatric Psychiatrics was to estimate the risk of hip fracture and ischemic stroke for users of individual NLs and ADs aged 65 years and older using signal detection analyses incorporating the high-dimensional propensity score (HDPS) methodology and to compare these risk estimates to the results of the cohort studies using survival analysis.

Methods

For each target-drug-event-combination (TDEC) a new-user design was used to identify incident users of either a target or a reference drug. Target drugs were the individual ADs and NLs under study. Reference drug in the class of NL was risperidone, reference for ADs was citalopram. Outcomes events were hip fracture and ischemic stroke.

The study period was set from January 1, 2004 through December 31, 2011. The source population was a random sample of 1,000,000 insurants aged 65 and older in 2005 of GePaRD. Individuals, who had been continuously enrolled in the database for at least a year without prescription of either the target or reference drug, entered the cohort on the day of the initial prescription of either the target or reference drug. The initial prescription also defined the exposure status. Individuals were excluded if target and reference drug were both prescribed on the day of cohort entry. Cohort exit was set as the first of the following dates: end or interruption of insurance status for more than three days, end of study period, 180th day of follow-up, or occurrence of an outcome event.

Within the baseline period (the year before cohort entry) the following variables were selected as potential covariates: all in- and outpatient diagnoses (3-digit codes), all in- and outpatient procedures (4-digit codes) and selected prescriptions (7-digit codes) which were used in the comparative safety study. The HDPS was estimated using 500 automatically selected covariates as well as the demographic covariates sex and age at cohort entry. A 1:1-nearest-neighbor caliper matching with a caliper of 0.05 was used to match an individual exposed to the reference drug to an individual exposed to the target drug. To verify the balancing of covariates in the matched cohort, absolute standardized differences (ASD) were calculated.

For each TDEC incidence rate ratios (IRRs) with 95% confidence intervals were estimated. Each IRR was treated as a potential signal, independent of the magnitude of the point estimate. Using the results of the cohort studies as gold standard, a signal was counted true positive, if aHR and IRR were both statistically significant with the same trend, and it was counted true negative if aHR and IRR were both not statistically significant. The quality of the signal detection approach was then expressed by calculating sensitivity and specificity, i.e. the number of true positive signals divided by the total number of statistically significant aHR and the number of true negative signals divided by the total number of not statistically significant aHR, respectively.

Results

HDPS matching considerably reduced the ASD; in 85.5% of the matched cohorts the ASD of all selected covariates was below 0.1. Results on aHRs were available for 82 TDECs. For 73 of these, IRRs could be calculated since enough drug users as well as cases remained after matching. Overall, sensitivity and specificity were 15.8% and 94.4%, respectively.

Conclusion

Due to the reduced source population the CIs of the IRRs were wider than those of the aHR of the cohort studies. Assuming the inadequate sensitivity was due to the small sample size, further analyses with the whole source population were planned. Nevertheless it was concluded, that this data-mining method has the potential to detect signals properly in an automated manner.

5.1 *Additional Analyses*

The signal detection analysis was repeated with the whole source population for the outcomes hip fracture and all-cause mortality. These were chosen since the aHRs showed the most statistically significant estimates of all outcomes. Estimates of IRRs were now available for all 82 TDECs. In 98.8% of the matched cohorts the ASD of all selected covariates was below 0.1. As expected, using the whole source population instead of a subsample of 1,000,000 insurants, the CIs of the IRRs were narrower and of similar width compared to those of the aHR of the cohort studies. In addition, more statistically significant estimates of the IRR were observed in comparison to the analysis based on the subsample. The best results, in terms of sensitivity and specificity, were seen for AD users regarding hip fracture (**Figure 5**). Overall, sensitivity and specificity were 77.1% and 93.6%, respectively. These results indicate that it is feasible to use claims databases such as GePaRD for the automatic monitoring of adverse reactions of newly marketed drugs. However, further research is needed before it can be applied routinely. The performance of the HDPS balancing needs to be enhanced and approval from the data owners (i.e. the SHIs) as well as their authorities has to be granted as the current legal situation does not allow the automated searches for unspecified TDECs.

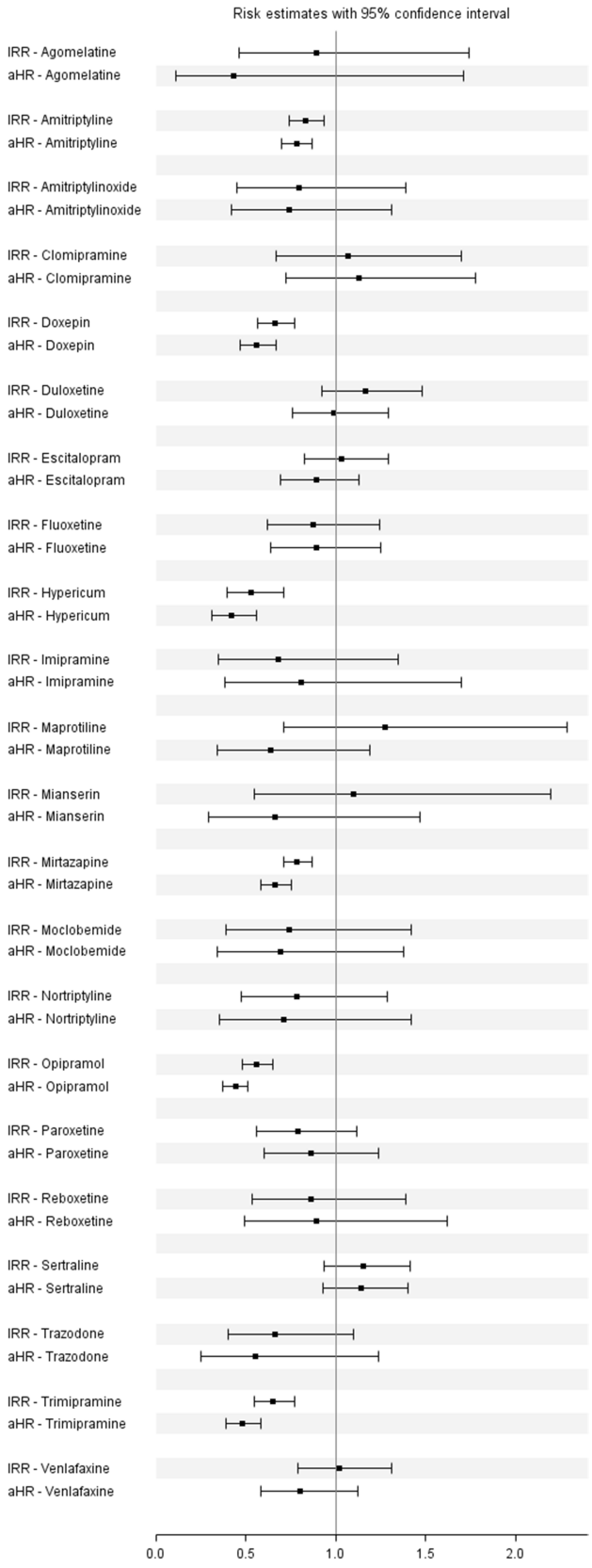

Figure 5 Comparison of incidence rate ratios (IRRs) and adjusted hazard ratios (aHRs) of hip fracture in user of antidepressants derived from signal detection analysis and survival analysis, respectively.

6 Overall Summary and Conclusion

In the DUS, we showed that NLs (6%) and especially ADs (12%) are prescribed to a large percentage of older persons in Germany. PIM NLs (1%) and ADs (5%) were often used prior to the publication of the PRISCUS list and warnings of public authorities between 2003 and 2005 regarding the use of NLs in elderly patients with dementia obviously did not have a major impact on the prescribing practice of physicians in routine care in Germany. Duration of therapy with ADs and especially NLs was relatively short and both drug classes were used for a broad range of indications.

Overall, the safety studies indicate that atypical NLs have a better safety profile compared to conventional NLs. Although we did not find differences for AMI, IS, PN and VTE, our study suggests that users of conventional NLs might be at higher risk for HF and HFR resulting in a higher risk of death compared to atypical NLs. On a substance level it is notable that for many outcomes, no differential risks were found for NLs that are frequently used in elderly patients, especially in dementia. With regard to the most important outcome all-cause mortality, haloperidol and levomepromazine were associated with a substantially increased risk of death compared to risperidone and should therefore not be used in elderly patients except in palliative care. Surprisingly, risperidone might be associated with a higher risk of death compared to many other NLs, although it is the only NL explicitly indicated to treat BPSD. If no substantial risk factors for falls and fractures exist, quetiapine might be an adequate treatment alternative. Our study also showed that the PRISCUS list has a clinical relevance for NLs, since PIM NLs were associated with a higher risk of HFR, PN, VTE and death and should be avoided whenever possible. Regarding AD use, we found no evidence that use of SSRIs is safer in elderly persons compared to TCAs. Overall, increased risks of HFR and – to a lesser extent – of all-cause mortality and IS were observed for SSRIs even in the more homogenous subgroups of patients with depression and opioid co-medication. On a substance level, citalopram seemed to be associated with comparatively high risks for most of the outcomes. A clear association between the outcomes and PIM ADs was only found with regard to all-cause mortality which yielded a comparatively high risk for the PIM amitriptyline. Surprisingly, an increased risk of hip fractures associated with PIM ADs could not be observed in our study, although many ADs were considered as PIM due to their possibly increased risk of falls and hip fractures.

With regard to the signal detection analysis, our results indicate that it is feasible to use claims databases such as GePaRD for the automatic monitoring of ADRs of newly marketed drugs. However, further research is needed before it can be applied routinely, e.g. the performance of the HDPS balancing needs to be enhanced and approval from the data owners

(i.e. the SHIs) as well as their authorities has to be granted as the current legal situation does not allow the automated searches for unspecified TDECs.

In conclusion, the use of claims data from GePaRD allowed investigating drug utilization patterns and the several safety outcomes in a cost-effective way and in a short time. Due to the large sample size, the safety evaluation of individual drugs was also possible for a representative sample of the elderly population in Germany. Therefore, this study illustrates that pharmacoepidemiological studies based on GePaRD are a useful tool to investigate drug utilization patterns and to monitor the safety of approved drugs in Germany.