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ORIGINAL ARTICLE

Polypharmacy, potentially inappropriate medication and pharmacogenomics drug exposure in the Rhineland Study

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Aim: High medication use may contribute to the efficiency of drug therapy in general, but it could also increase the burden of adverse drug reactions. We aimed to assess medication use and the prevalence of three risk factors for adverse drug reactions: the use of polypharmacy, potentially inappropriate medication in the elderly and pharmacogenomic polymorphisms affecting the metabolism of drugs.

Methods: Cross-sectional interview-based medication data (including over-the-counter drugs) was collected in a large population-based cohort (≥30 years of age) in Bonn, Germany.

Results: Analyses were based on the first 5000 participants of the Rhineland Study (mean age 55 years, 57% women). Of our participants, 66.0% reported the use of a drug regularly, which increased to 87.4% in participants aged ≥65 years (n = 1301). The rates of use of polypharmacy, potentially inappropriate medication and pharmacogenomic drugs were 15.9%, 6.4% and 20.5%, respectively. In participants <65 years, 16.0% (95% CI 14.8, 17.3) had at least one risk factor. In participants aged ≥65 years, 54.1% (95% CI 51.4, 56.8) had at least one and 27.4% (95% CI 25.0, 29.9) had at least two risk factors. Extrapolating these numbers to the German population implies that around 9 million of the 17 million individuals aged 65 years or older are potentially at an elevated risk for adverse drug reactions, of which 4.6 million are at a potentially highly elevated risk for adverse drug reactions.

Conclusion: Our study shows that drug use is common and the individual risk for an adverse drug reaction in our population is high. This suggests room for improvement in general medication use.

KEYWORDS
adverse drug reactions, drug utilization, pharmacoepidemiology, pharmacogenomics, quality use of medicine

1 | INTRODUCTION

Due to population aging, increased availability of effective treatments and increased emphasis on preventive treatments, long-term medication use in Western countries is high and rising.[1–6] While this may

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contribute to efficiency of drug therapy in general, it may also lead to an increased risk of adverse drug reactions (ADRs). In Germany, medication use is high and the burden of ADRs is substantial, with 6.5% of emergency admissions being caused by suspected ADRs.[3,7]

The use of multiple drugs, polypharmacy, is a risk factor for ADRs.[8] A population-based study from the United States reported that outpatients taking five or more drugs had an 80% increased risk of experiencing an ADR compared to patients taking fewer drugs.[9] Prevalence rates of polypharmacy, defined as the use of five or more drugs, are around 40% in older (≥65 years) German populations and comparable to other countries.[2–6,10–12] Data is mostly based on claims data and therefore lacks information on over-the-counter drugs and the ability to identify concurrent drug use. Polypharmacy rates that include over-the-counter drugs are from 2008-2011 and most likely not representative anymore.[3]

The use of potentially inappropriate medication (PIM) is associated with a higher risk for ADRs.[13,14] Potentially inappropriate drugs are drugs whose risk for ADRs exceeds their expected clinical benefit when given to older individuals and which have a better-tolerated alternative.[15] This is particularly for older individuals because aging is associated with altered pharmacokinetics and pharmacodynamics, such as delayed renal clearance, which increases the risk for adverse events.[16] The Beers list is the most used list of PIMs.[17] The Beers list was established by the American Geriatrics Society and also includes drugs that are not available in Europe, making this tool less suitable for analysing German prescriptions. In Germany, PIMs are identified with the PRISCUS list (Latin for "old and venerable"). Comparable to the Beers list, the PRISCUS list contains PIMs. The PRISCUS list, however, is specifically based on the German drug market.[18] The use of PIMs was reportedly around 20-25% in German populations aged 65 or older.[11,18–21] These reports on PIM use in Germany were conducted before the release of the PRISCUS list in 2010 and mostly did not reflect continuous PIM use. A report on data collected between 2009 and 2014 from the Berlin Aging Study II, which was a cohort of 1382 older and predominantly healthy adults, showed that 5.9% of participants were using a PIM according to the PRISCUS list.[22] From this report, however, it is unclear whether this was regularly used medication. It has been reported in a German cohort study based on claims data that the use of PIMs compared to PIM alternatives was associated with an increased risk of hospitalization (6% attributable risk).[23] An Italian retrospective population-based cohort study found a 16% increased risk for hospitalization when comparing individuals exposed to PIMs to individuals not exposed to PIMs.[24] This shows the need for avoiding or monitoring PIM use in older individuals.

Finally, genetic variability can affect the exposure or safety of specific drugs, herein called pharmacogenomics (PGX) drugs. The use of PGX drugs could substantially increase the risk for ADRs.[25,26] Recently a study analysing ADR-related hospital admissions in Germany reported that higher activity of CYP2C19 was associated with having a clopidogrel-related ADR.[27] The impact of PGX drugs on the risk for ADRs depends on the prevalence of PGX drug use and the prevalence of actionable genotypes. The prevalence of actionable genotypes is high; it was 99% in a population from the United States when considering CYP2C9, CYP2C19, CYP2D6, SLCO1B1 and VKORC1.[28] Not much is known about the prevalence of PGX drug use and the definition of a PGX drug is inconsistent. In the Netherlands, 24% of the total drugs used between 2011 and 2017 were PGX drugs.[29] Classified as PGX drugs were drugs listed by the Dutch Pharmacogenetics Working Group (DPWG). A study from the United States reported that half of the people started at least one PGX drug between 2009 and 2012, with drugs that were already used before the start of the study not taken into account.[30] In this study, drugs listed by the DPWG and/or the Clinical Pharmacogenetics Implementation Consortium (CPIC) were classified as PGX drugs. A study from Denmark reported that 30% of the older patients (65-79 years) received at least one prescription for a PGX drug (based on DPWG and CPIC) in 2017.[31] There are no reports on frequency of PGX drugs use in the general population in Germany.

We are not aware of any study that has reported on the distribution and co-occurrence of polypharmacy, PIM use and PGX use. For clinical practice it is important to know how risk factors for potential ADRs are distributed. Better insight into individual patient risk factors could possibly decrease the burden of ADRs in real-world conditions. We therefore aimed to assess, in a general population sample, medication use and the prevalence of three important risk factors for potential ADRs: (a) polypharmacy, (b) the use of PIMs and (c) the use of PGX drugs. Moreover, we assessed the pattern of co-occurrence of these three risk factors. Finally, we compared individuals younger than 65 years of age with individuals aged 65 years or older.

What is already known about this subject

- Use of polypharmacy, potentially inappropriate medication and pharmacogenomic drugs may be common important risk factors for adverse drug reactions.
- The distribution and co-occurrence of these risk factors is unknown.
- Such knowledge is important as better insight into individual patient risk factors may decrease the occurrence of adverse drug reactions.

What this study adds

- Among participants aged ≥65 years, 54.1% had at least one and 27.4% had at least two risk factors.
- Around 9 million of the 17 million individuals aged ≥65 years in Germany potentially have an elevated risk for adverse drug reactions and 4.6 million potentially have a highly elevated risk.

2 | METHODS

2.1 | Study design and setting

This cross-sectional study was performed in the first 5000 participants of the Rhineland Study. The Rhineland Study is a single-centre prospective community-based cohort study that started recruitment in 2016. The primary focus of the study is on aging and age-related brain disorders in adult life. Brain development and maturation extends well into the third decade of life. Therefore, we only included adults aged 30 years or older. Our source population consists of all inhabitants aged 30 years or older in geographically defined areas in Bonn, Germany. The municipality provides contact details of all eligible people in the designated areas. Potential participants receive an invitation via mail. Participation is only possible upon invitation and regardless of health status. The only exclusion criteria for the study is an inability to sufficiently understand the informed consent. We will follow participants for decades with re-examinations taking place every 3-4 years.

Approval to undertake the study was obtained from the ethics committee of the University of Bonn Medical Faculty. We obtained written informed consent from all participants in accordance with the Declaration of Helsinki.

2.2 | Medication data collection

Participants were asked to bring the original packages of the drugs (including over-the-counter drugs and excluding homeopathic drugs) and prescribed supplements that they currently use and that they used *as needed* during the past year. Over-the-counter *as needed* medication that was used <10 days during the past year was not taken into account. Medication use was assessed in an interview form with the use of a software instrument for database-assisted online collection of medication data (Instrument zur Datenbank gestützten Online-Erfassung von Medikamenten, IDOM).[32] The IDOM software is linked to a database provided by the Research Institute of the Federal Association of regional statutory health insurance funds in Germany (Wissenschaftliches Institut der Ortskrankenkassen, WIdO), which contains information on all drugs available on the German market.[33] For every preparation, the type of use, either regularly or *as needed* (pro re nata, PRN), is registered. Regular use is defined as use in a specific time pattern regardless of symptoms. Use based on the occurrence of symptoms was defined as *as needed* use. For every drug or supplement, the name, dosage, Anatomical Therapeutic Chemical (ATC) code[34] and prescription status were also registered. For *as needed* used drugs and supplements, the frequency of use during the past year was recorded.

2.3 | 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, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[35]

2.4 | Polypharmacy

Polypharmacy was defined as the regular use of five or more drugs or prescribed supplements concomitantly. Additionally, we determined prescribed polypharmacy, which was defined as the regular use of five or more drugs or supplements prescribed by a physician. For combination preparations, the active substances were counted separately.

2.5 | Potentially inappropriate medication

Medications listed on the PRISCUS list were defined as PIMs.[18] The use of PIMs was assessed in all participants. PIM use was only counted as a risk factor for potential ADRs in participants aged 65 years or older since the PRISCUS-list was designed for this age group. Analyses were done for regularly used drugs only, and for regularly and *as needed* used drugs combined.

2.6 | PGX drugs

The selection of PGX drugs was based on CPIC and DPWG guidelines.[36] We selected drugs (Appendix I) for which pharmacogenomic testing is recommended for the following genes: CYP2C9, CYP2C19, CYP2D6, SLCO1B1 and VKORC1. We selected these genes because polymorphisms of them are highly prevalent and because they influence the metabolism of drugs commonly taken in primary care.[29,30] Analyses were done for regularly used drugs only, and for regularly and *as needed* used drugs combined.

2.7 | Data analysis

First we describe the top 15 of drug categories (based on the second level of the ATC code[34]; fixed-dose combinations were split into their constituent active substances, therefore exposure was counted for each active substance) in our study population, separately for women and men and for regular and *as needed* drug use (if used 10 days or more during the last year). Since <7% of the regularly used drugs were without a prescription, no distinction was made between prescribed and nonprescribed drugs. The prevalence of the three major risk factors for potential ADRs, (a) polypharmacy and prescribed polypharmacy, (b) the use of PIMs and (c) use of PGX drugs, was assessed, differentiated by gender and age groups. Furthermore, the number of risk factors for potential ADRs per participant was determined. Prevalence measures are presented with 95% confidence intervals. Participants with incomplete medication data were excluded from the analyses. The analyses were performed using R version 3.4.3.[37]

3 | RESULTS

In total, 4782 out of 5000 participants were included in the analyses. A total of 218 (4.4%) participants were excluded because of missing medication data. Participants were on average 55.1 years old (standard deviation [SD] 14.0 years, range 30-95) and 56.6% of them were women (excluded participants: mean age = 55.4, 54.1% (n = 118) women). The age-gender distribution of our population reflects that of the overall German population in the corresponding age classes[38] (Appendix II).

3.1 | Overview of medication use

In total, 66.0% (n = 3154) of the participants reported the use of at least one preparation regularly. This increased to 87.4% (n = 1137) in participants aged 65 years or older (total n = 1301). Use of at least one preparation *as needed* during the past year was reported by 70.5% (n = 3370) of the participants.

Figure 1 shows the 15 most common regularly taken drug classes in women and men. For both women and men, five drug classes belong to the cardiovascular system group. Thyroid therapy (ATC code starting with H03) was most frequently used (34.9%, n = 944) in women, whereas in men the renin system agents (ATC code starting with C09) were the most often used drugs (23.4%, n = 485). An overview of the most common *as needed* used drugs (only including drugs used ≥10 during the last year) can be found in Appendix III, with the frequency of use during the past year. Most participants reported *as needed* use of painkillers (ATC code starting with M01).

3.2 | Polypharmacy

The overall prevalence of polypharmacy (defined as the concurrent use of ≥5 drugs or prescribed supplements) was 15.9% (n = 759) and for prescribed polypharmacy 14.5% (n = 693). The prevalence of polypharmacy and prescribed polypharmacy increased with age similarly for women and men (Figure 2).

In the group of participants aged 65 or older 37.1% (n = 483) were on polypharmacy and 34.1% (n = 444) were on prescribed polypharmacy. In the participants aged <65 years, 7.9% (n = 276) were on polypharmacy and 7.2% (n = 249) were on prescribed polypharmacy.

3.3 | Potentially inappropriate medication

In total, 6.4% (n = 83) of the participants aged 65 years or older (total n = 1301) were regularly using at least one PIM. This was higher compared to participants aged <65 years (2.5%, n = 86) (Table 1). Within the age group 80-89, there was a significant difference in gender with regard to regular PIM use (women 19.8%, men 5.5%, $P = 0.003$). PIM use in women aged 65 years or older was mainly caused by the use of antidepressants (amitriptyline n = 13 and fluoxetine n = 6), antiarrhythmic drugs (flecainide n = 7) and drugs to treat an overactive bladder (solifenacin n = 8). When taking into account both regular and *as needed* used drugs 10.8% (n = 141) of the participants aged 65 years or older were using at least one PIM. Please see Appendix IV for the number of users per specific drug.

3.4 | Pharmacogenetics

In total, 20.5% (n = 981) of the participants regularly used at least one PGX drug. These were mainly PGX drugs that are influenced by SLCO1B1 (10.1%, n = 484), CYP2C19 (9.3%, n = 446) and CYP2D6 (5.8%, n = 278) polymorphisms. The use of these PGX drugs increased with increasing age (Table 2). There was higher PGX drug use in men compared to women (women 19.2%, men 22.2%; $P = 0.01$). When looking at the PGX drugs for specific genes separately, there was a higher use of PGX drugs influenced by SLCO1B1 polymorphisms in

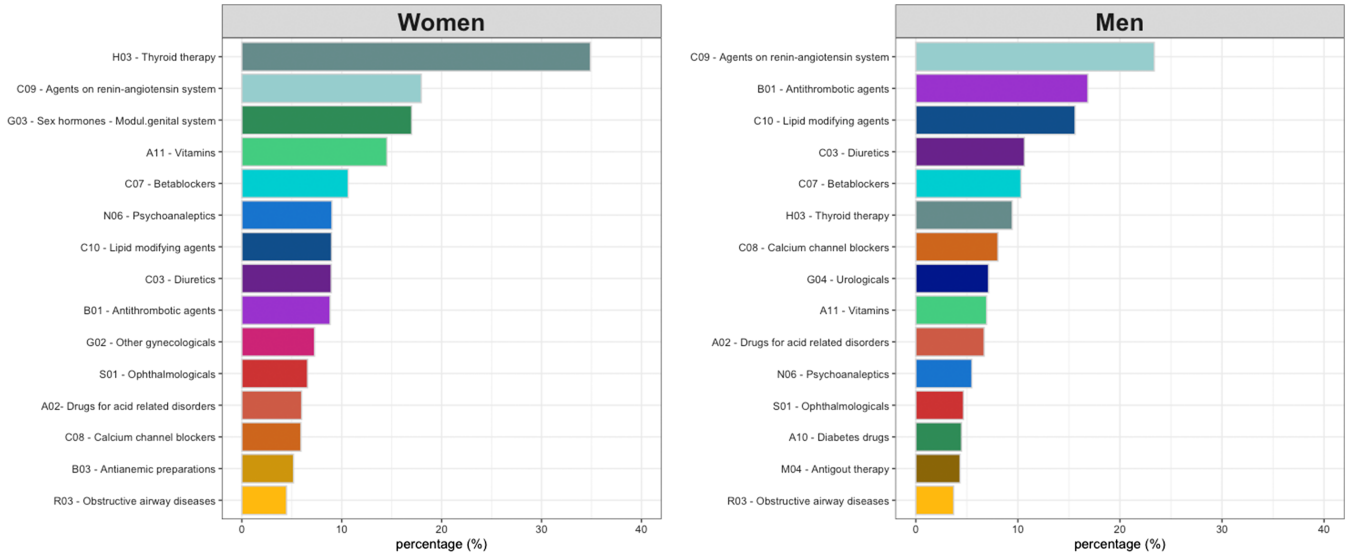

FIGURE 1 Top 15 of regularly used drugs for women and men

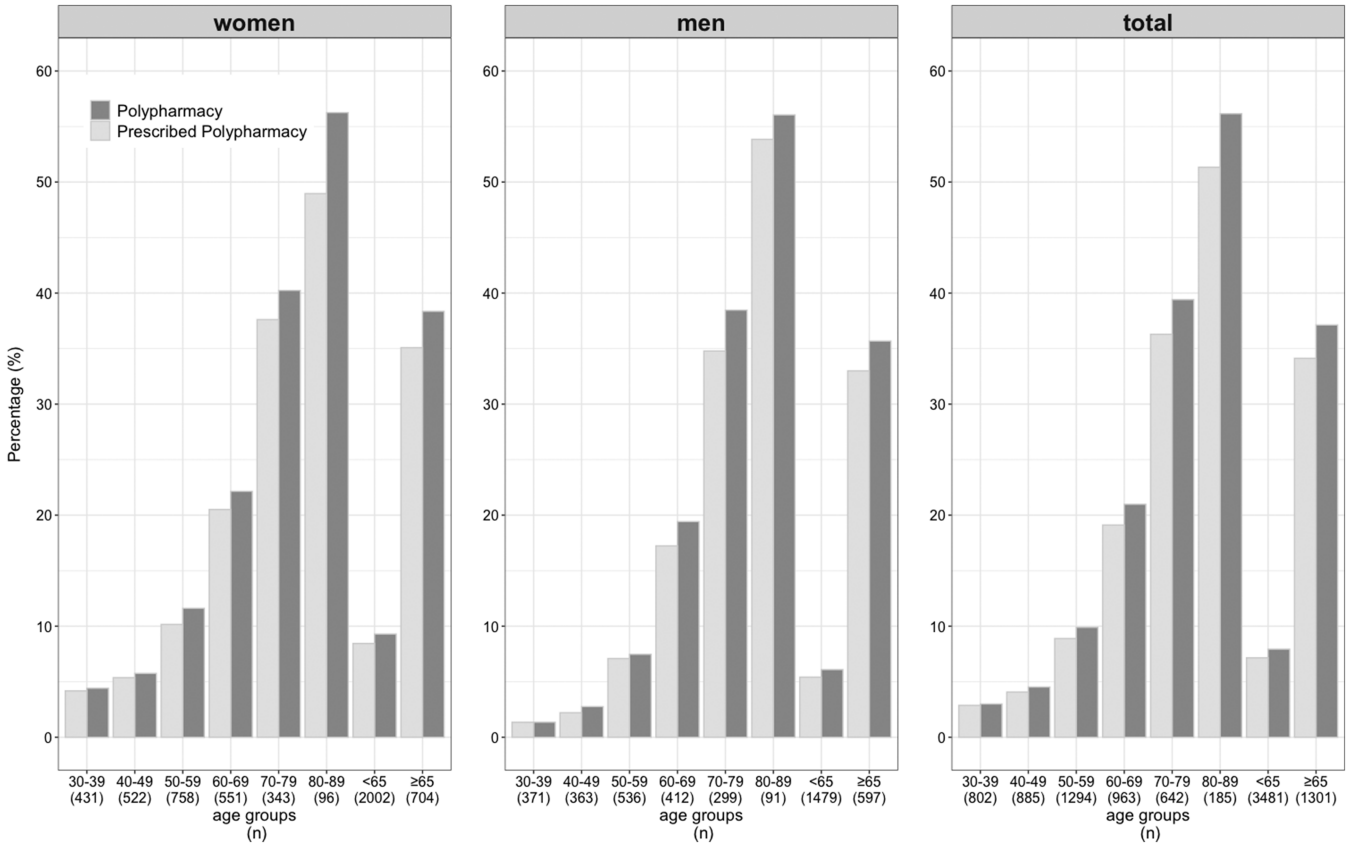

FIGURE 2 The prevalence of polypharmacy (using ≥5 drugs regularly) and prescribed polypharmacy, categorized by gender and age

men compared to women for the age groups 40-49 (women 0.2%, men 3.0%; $P < 0.01$), 50-59 (women 4.4%, men 8.2%; $P < 0.01$) and 70-79 (women 19.0%, men 36.8%; $P = <0.01$). This reflects the higher statin use in men in these age groups. There was a higher use of PGX drugs influenced by CYP2D6 polymorphisms in women compared to men in the age group 50-59 (women 8.2%, men 2.6%; $P = <0.01$). This was mainly due to more frequent use of antidepressants (women n = 29, men n = 6) and tamoxifen (women n = 24, men n = 0) in women compared to men in this age group.

In the group of participants aged 65 years or older 41.6% (n = 541) regularly used at least one PGX drug, whereas 12.6% (n = 440) of participants younger than 65 years of age did. See Appendix V for data that includes both regular and *as needed* used drugs, and Appendix I for the number of users per specific drug.

3.5 | Risk factors for adverse drug reactions

In participants younger than 65 years, 16.0% (n = 559) had at least one out of two risk factors for potential ADRs (Appendix V). In participants aged 65 or older 54.1% (n = 704) had at least one out of three risk factors and 27.4% (n = 357) of the participants had at least two of the risk factors. The prevalence and number of risk factors strongly increased with age (Figure 3). Within the age group 80-89, having all three risk factors was more frequent among women than men (women 13.5%, men 2.2%; $P = <0.01$). See Appendix V for data on the number of risk factors when including both regular and *as needed* used drugs.

4 | DISCUSSION

We assessed the prevalence of drug intake in the population-based cohort of the Rhineland Study with the aim of identifying major general risks for the susceptibility to potential ADRs in a normal population of individuals aged 30 years and above. The prevalence of regular drug intake in general was 66.0% and 70.5% for *as needed* medication use. About 16% of the population was exposed to polypharmacy, meaning they took five or more drugs concomitantly.

Having at least one of the selected risk factors for ADRs was 16.0% in participants younger than 65 years of age and 54.1% in participants aged 65 years or older. In the population aged 65 years or older, 27.4% had at least two risk factors. Extrapolated for Germany, this would mean that out of the 17 million inhabitants aged 65 years or older, around 9 million individuals are potentially at an elevated risk for ADRs, with around 4.6 million of those potentially at a highly elevated risk for ADRs. Especially in light of the rapidly increasing older population, this could have major consequences for public health.

Comparable to a previous study performed in Germany, the most used drug classes were cardiovascular system drugs.[3] However, in

TABLE 1 The use of potentially inappropriate medication, categorized by gender, age and the type of use (regular or regular and *as needed*)

Potentially inappropriate medication use		Age group								
Regular use		**30-39 n = 802**	**40-49 n = 885**	**50-59 n = 1294**	**60-64 n = 500**	**65-69 n = 463**	**70-79 n = 642**	**80-89 n = 187**	**<65 n = 3481**	**≥ 65 n = 1301**
Women	n	6	12	33	9	11	26	19	60	56
	%	1.4%	2.3%	4.3%	3.1%	4.2%	7.6%	19.8%	3.0%	8.0%
	95% CI	(0.3, 3.6)	(1.0, 3.6)	(2.9, 5.8)	(1.1, 5.1)	(1.8, 6.7)	(4.8, 10.4)	(11.8, 27.8)	(2.2, 3.7)	(6.0, 10.0)
Men	n	4	7	10	5	8	14	5	26	27
	%	1.1%	1.9%	1.9%	2.4%	3.9%	4.7%	5.5%	1.8%	4.5%
	95% CI	(0.0, 2.1)	(0.7, 3.0)	(0.7, 3.0)	(0.3, 4.5)	(1.3, 6.6)	(1.3, 7.1)	(0.8, 10.2)	(1.1, 2.4)	(2.9, 6.2)
Total	n	10	19	43	14	19	40	24	86	83
	%	1.2%	2.1%	3.3%	2.8%	4.1%	6.2%	12.8%	2.5%	6.4%
	95% CI	(0.5, 2.0)	(1.2, 3.1)	(2.3, 4.3)	(1.4, 4.2)	(2.3, 5.9)	(4.4, 8.1)	(8.0, 17.6)	(2.0, 3.0)	(5.1, 7.7)
Regular and as needed use		**30-39**	**40-49**	**50-59**	**60-64**	**65-69**	**70-79**	**80-89**	**<65**	**≥ 65**
		n = 802	n = 885	n = 1294	n = 500	n = 463	n = 642	n = 187	n = 3481	n = 1301
Women	n	13	25	54	23	16	52	23	115	91
	%	3.0%	4.9%	7.1%	7.9%	6.2%	15.2%	24.0%	5.7%	12.9%
	95% CI	(1.4, 4.6)	(3.0, 6.6)	(5.3, 8.9)	(4.8, 11.0)	(3.2, 9.1)	(11.4, 19.0)	(15.4, 32.5)	(4.7, 6.8)	(10.4, 15.4)
Men	n	16	14	21	7	14	28	8	58	50
	%	4.3%	3.9%	3.9%	3.3%	6.9%	9.4%	8.8%	3.9%	8.4%
	95% CI	(2.2, 6.3)	(1.9, 5.8)	(2.3, 5.6)	(0.9, 5.8)	(3.4, 10.4)	(6.1, 12.7)	(3.0, 14.6)	(2.9, 4.9)	(6.2, 10.6)
Total	n	29	39	75	30	30	80	31	173	141
	%	3.6%	4.4%	5.8%	6.0%	6.5%	12.5%	16.6%	5.0%	10.8%
	95% CI	(2.3, 4.9)	(3.1, 5.8)	(4.5, 7.1)	(3.9, 8.1)	(4.2, 8.7)	(9.9, 15.0)	(11.2, 21.9)	(4.2, 5.7)	(9.1, 12.5)

CI, confidence interval.

contrast to that study 10% of our participants used diuretics (ATC code starting with C03) whereas this was <5% in their study. This is probably because we have split fixed-dose combinations into their constituent active substances. Diuretics are often used in fixed-dose combinations, for which the ATC code often does not start with C03.[34] Thyroid therapy use was very high in our study, mainly in women. This may partly be due to regional differences in thyroid disease and a slight overrepresentation of middle-aged women in our population.[39,40] Furthermore, German general practitioners may be more likely to prescribe thyroid therapy in case of subclinical hypothyroidism than general practitioners in other countries.[41]

The use of polypharmacy was high in our population. Compared to earlier studies of Knopf et al[3] and Thürmann et al[11] we found a lower prevalence of polypharmacy. This could be because we looked at drugs and supplements that were reported to be used regularly. Knopf et al did not distinguish between regular and *as needed* use. Thürmann et al used claims data, which also makes it difficult to distinguish between regular and *as needed* used drugs. Additionally, claims data give no insight into actual drug use. We expect our results, based on interview data, to better reflect real-world conditions. Compared to Kostev et al[10] we found higher rates of polypharmacy. A likely explanation for this discrepancy is that the use of general practitioner data in that study led to incomplete medication records. The discrepancy between patient records and medication data from patient interviews could lead to important information on ADR risks. Polypharmacy is not per definition inappropriate, however, with a use of 37.1% in older participants in our study, there may be substantial room for reductions in drug prescribing and thereby reduction of ADR risk.

In our study, PIM use was higher in women compared to men in participants aged 80-89 years. Higher PIM use in women was also found in other studies.[19,20] This is likely because drugs listed on the PRISCUS list are typically used for indications that are more prevalent in older women compared to older men, such as urine incontinence and depression.[42–44] Use of PIMs was in our study lower than the annual prevalence found in German studies (20-25%) based on data from before the release of the PRISCUS list.[11,18–21] One German study also collected data cross-sectionally and partly after the release of the PRISCUS list, and their results were comparable to ours. It is unclear, however, whether *as needed* used drugs were also included in their study. We reported that the use of PIMs was lower in the participants aged <65 years compared to participants aged 65 years or older (2.5% *vs* 6.4%). It is unlikely that the lower rate of PIM use in our study compared to reports from before 2010 is due to the recommendations made in the PRISCUS list. It is rather because the PRISCUS list in general contains old drugs that are substituted by better ones. In

TABLE 2 The regular use of PGX drugs, categorized by gender and age

		Age group							
CYP2C9		**30-39 n = 802**	**40-49 n = 885**	**50-59 n = 1294**	**60-69 n = 963**	**70-79 n = 642**	**80-89 n = 185**	**<65 n = 3481**	**≥ 65 n = 1301**
Women	n	1	1	7	4	3	1	11	6
	%	0.2%	0.2%	0.9%	0.7%	0.9%	1.0%	0.5%	0.9%
	95% CI	(0.0, 0.7)	(0.0, 0.6)	(0.2, 1.6)	(0.0, 1.4)	(0.0, 1.9)	(0.0, 3.1)	(0.2, 0.9)	(0.2, 1.5)
Men	n	2	2	6	7	2	1	13	7
	%	0.5%	0.6%	1.1%	1.7%	0.7%	1.1%	0.9%	1.2%
	95% CI	(0.0, 1.3)	(0.0, 1.3)	(0.2, 2.0)	(0.5, 2.9)	(0.0, 1.6)	(0.0, 3.2)	(0.4, 1.4)	(0.3, 2.0)
Total	n	3	3	13	11	5	2	24	13
	%	0.4%	0.3%	1.0%	1.1%	0.8%	1.1%	0.7%	1.0%
	95% CI	(0.0, 0.8)	(0.0, 0.7)	(0.5, 1.5)	(0.5, 1.8)	(0.1, 1.5)	(0.0, 2.5)	(0.4, 1.0)	(0.5, 1.5)
CYP2C19		**30-39**	**40-49**	**50-59**	**60-69**	**70-79**	**80-89**	**<65**	**≥ 65**
		n = 802	n = 885	n = 1294	n = 963	n = 642	n = 185	n = 3481	n = 1301
Women	n	10	21	70	62	66	28	130	127
	%	2.3%	4.0%	9.2%	11.3%	19.2%	29.2%	6.5%	18.0%
	95% CI	(0.9, 3.7)	(2.3, 5.7)	(7.2, 11.3)	(8.6, 13.9)	(15.1, 23.4)	(20.1, 38.3)	(5.4, 7.6)	(15.2, 20.9)
Men	n	13	18	36	46	55	20	93	96
	%	3.5%	5.0%	6.7%	11.2%	18.4%	22.0%	6.3%	16.1%
	95% CI	(1.6, 5.3)	(2.7, 7.2)	(4.6, 8.8)	(8.1, 14.2)	(14.0, 22.8)	(13.5, 30.5)	(5.0, 7.5)	(13.1, 19.0)
Total	n	23	39	106	108	121	48	223	223
	%	2.9%	4.4%	8.2%	11.2%	18.8%	25.7%	6.4%	17.1%
	95% CI	(1.7, 4.0)	(3.1, 5.8)	(6.7, 9.7)	(9.2, 13.2)	(15.8, 21.9)	(19.4, 31.9)	(5.6, 7.2)	(15.1, 19.2)
CYP2D6		**30-39**	**40-49**	**50-59**	**60-69**	**70-79**	**80-89**	**<65**	**≥ 65**
		n = 802	n = 885	n = 1294	n = 963	n = 642	n = 185	n = 3481	n = 1301
Women	n	8	15	62	42	42	20	108	81
	%	1.9%	2.9%	8.2%	7.6%	12.2%	20.8%	5.4%	11.5%
	95% CI	(0.6, 3.1)	(1.4, 4.3)	(6.2, 10.1)	(5.4, 9.8)	(8.8, 15.7)	(12.7, 29.0)	(4.4, 6.4)	(9.1, 13.9)
Men	n	4	11	14	23	26	10	40	49
	%	1.1%	3.0%	2.6%	5.6%	8.7%	11.0%	2.7%	8.2%
	95% CI	(0.0, 2.1)	(1.3, 4.8)	(1.3, 4.0)	(3.4, 7.8)	(5.5, 11.9)	(4.6, 17.4)	(1.9, 3.5)	(6.0, 10.4)
Total	n	12	26	76	65	68	30	148	130
	%	1.5%	2.9%	5.9%	6.7%	10.6%	16.0%	4.3%	10.0%
	95% CI	(0.7, 2.3)	(1.8, 4.1)	(4.6, 7.2)	(5.2, 8.3)	(8.2, 13.0)	(10.8, 21.3)	(3.6, 4.9)	(8.4, 11.6)
SLCO1B1		**30-39**	**40-49**	**50-59**	**60-69**	**70-79**	**80-89**	**<65**	**≥ 65**
		n = 802	n = 885	n = 1294	n = 963	n = 642	n = 185	n = 3481	n = 1301
Women	n	0	1	33	70	65	32	62	140
	%	0.0%	0.2%	4.4%	12.7%	19.0%	33.3%	3.1%	19.9%
	95% CI	(0.0, 0.0)	(0.0, 0.6)	(2.9, 5.8)	(9.9, 15.5)	(14.8, 23.1)	(23.9, 42.8)	(2.3, 3.9)	(16.9, 22.8)
Men	n	3	11	44	77	110	36	84	198
	%	0.8%	3.0%	8.2%	18.7%	36.8%	39.6%	5.7%	33.2%
	95% CI	(0.0, 1.7)	(1.3, 4.8)	(5.9, 10.5)	(14.9, 22.5)	(31.3, 42.3)	(29.5, 49.6)	(4.5, 6.9)	(29.4, 36.9)
Total	n	3	12	77	147	175	68	146	338
	%	0.4%	1.4%	6.0%	15.3%	27.3%	36.4%	4.2%	26.0%
	95% CI	(0.0, 0.8)	(0.6, 2.1)	(4.7, 7.2)	(13.0, 17.5)	(23.8, 30.7)	(29.5, 43.3)	(3.5, 4.9)	(23.6, 28.4)
VKORC1		**30-39**	**40-49**	**50-59**	**60-69**	**70-79**	**80-89**	**<65**	**≥ 65**
		n = 802	n = 885	n = 1294	n = 963	n = 642	n = 185	n = 3481	n = 1301

TABLE 2 (Continued)

CYP2C9		Age group							
		30-39 n = 802	**40-49 n = 885**	**50-59 n = 1294**	**60-69 n = 963**	**70-79 n = 642**	**80-89 n = 185**	**<65 n = 3481**	**≥ 65 n = 1301**
Women	n	0	2	0	1	4	3	2	9
	%	0.0%	0.4%	0.0%	0.2%	1.2%	3.1%	0.1%	1.3%
	95% CI	(0.0, 0.0)	(0.0, 0.9)	(0.0, 0.0)	(0.0, 0.5)	(0.0, 2.3)	(0.0, 6.6)	(0.0, 0.2)	(0.4, 2.1)
Men	n	0	1	4	6	14	3	10	18
	%	0.0%	0.3%	0.7%	1.5%	4.7%	3.3%	0.7%	3.0%
	95% CI	(0.0, 0.0)	(0.0, 0.8)	(0.0, 1.5)	(0.3, 2.6)	(2.3, 7.1)	(0.0, 7.0)	(0.3, 1.1)	(1.6, 4.4)
Total	n	0	3	4	7	18	6	12	27
	%	0.0%	0.3%	0.3%	0.7%	2.8%	3.2%	0.3%	2.1%
	95% CI	(0.0, 0.0)	(0.0, 0.7)	(0.0, 0.6)	(0.2, 1.3)	(1.5, 4.1)	(0.7, 5.7)	(0.2, 0.5)	(1.3, 2.8)
Any		**30-39**	**40-49**	**50-59**	**60-69**	**70-79**	**80-89**	**<65**	**≥ 65**
		n = 802	n = 885	n = 1294	n = 963	n = 642	n = 185	n = 3481	n = 1301
Women	n	16	37	130	139	139	57	246	274
	%	3.7%	7.1%	17.2%	25.2%	40.5%	59.4%	12.3%	38.9%
	95% CI	(1.9, 5.5)	(4.9, 9.3)	(14.5, 19.8)	(21.6, 28.9)	(35.3, 45.7)	(49.6, 69.2)	(10.8, 13.7)	(35.3, 42.5)
Men	n	18	37	86	123	147	49	194	267
	%	4.9%	10.2%	16.0%	29.9%	49.2%	53.8%	13.1%	44.7%
	95% CI	(2.7, 7.0)	(7.1, 13.3)	(12.9, 19.2)	(25.4, 34.3)	(43.5, 54.8)	(43.6, 64.1)	(11.4, 14.8)	(40.7, 48.7)
Total	n	34	74	216	262	286	106	440	541
	%	4.2%	8.4%	16.7%	27.2%	44.5%	56.7%	12.6%	41.6%
	95% CI	(2.8, 5.6)	(6.5, 10.2)	(14.7, 18.7)	(24.4, 30.0)	(40.7, 48.4)	(48.6, 63.8)	(11.5, 13.7)	(38.9, 44.3)

CI, confidence interval; CYP, cytochrome P450.

addition, most studies were based on claims data and therefore also contain hospitalized and nursing home residents, for whom PIM use is especially high. Note, however, that the use of PIMs in a highly controlled setting such as a hospital or nursing home is less risky than the use of PIMs in an uncontrolled home setting.

We assessed PIM use with the PRISCUS list, which is established for the German market specifically. Our results might therefore not be generalizable to other populations. A study comparing five different PIM lists in a Swedish population showed that the prevalence of PIM use was comparable between lists, varying from 16% (Norwegian General Practice criteria) to 24% (2012 Beers criteria). Surprisingly, only 14% of the PIM users were covered by each of the five PIM lists applied. This reflects the small overlap in their content, which complicates comparing the association of different PIM lists with clinical outcomes like ADRs.[45]

In our study, the use of PGX drugs was high at 20.2%. This is in accordance with reports from the Netherlands, where 24% of the total drugs used between 2011 and 2017 were PGX drugs.[25] Within that Dutch population, genotyping SLCO1B1, CYP2C19 and CYP2D6 would cover all possible drug-gene interactions for 95% of the drugs used in the Netherlands.[29] Drugs that are influenced by SLCO1B1, CYP2C19 and CYP2D6 polymorphisms also caused the high prevalence of PGX drug use in our study. This was mainly due to frequent use of antidepressants, statins and proton pump inhibitors. PGX drugs that are influenced by VKORC1 are mainly vitamin K antagonists. Since the use of vitamin K antagonists is decreasing because of increased use of nonvitamin K oral anticoagulants, the importance of VKORC1 genotyping will probably decrease further.[46] Genotyping CYP2C9 could be of importance, however, as this polymorphism influences the metabolism of over-the-counter painkillers that are widely used *as needed* without consultation with a physician. For example, around 23% of the participants in our study reported the use of ibuprofen *as needed*. The fact that PGX drugs are frequently used in the German population shows the potential benefit of pre-emptive pharmacogenetic genotyping, especially of SLCO1C1, CYP2C19 and CYP2D6, to reduce potential ADRs and increase beneficial drug outcomes.

We report on the co-occurrence of three major general risks for the susceptibility to potential ADRs in the general, nonhospitalized population: polypharmacy, PIM use and PGX drug use. We found a high co-occurrence of these risk factors for potential ADRs. Although these three risk factors separately seem to increase the risk for different groups in the population, having multiple risk factors might not only lead to an addition of risks for potential ADRs, but could very likely potentiate the risk. Especially within more vulnerable groups, as, for example, patients with renal dysfunction that use PIM or poor metabolizers that use PGX drugs, additionally being exposed to polypharmacy might even be more harmful.

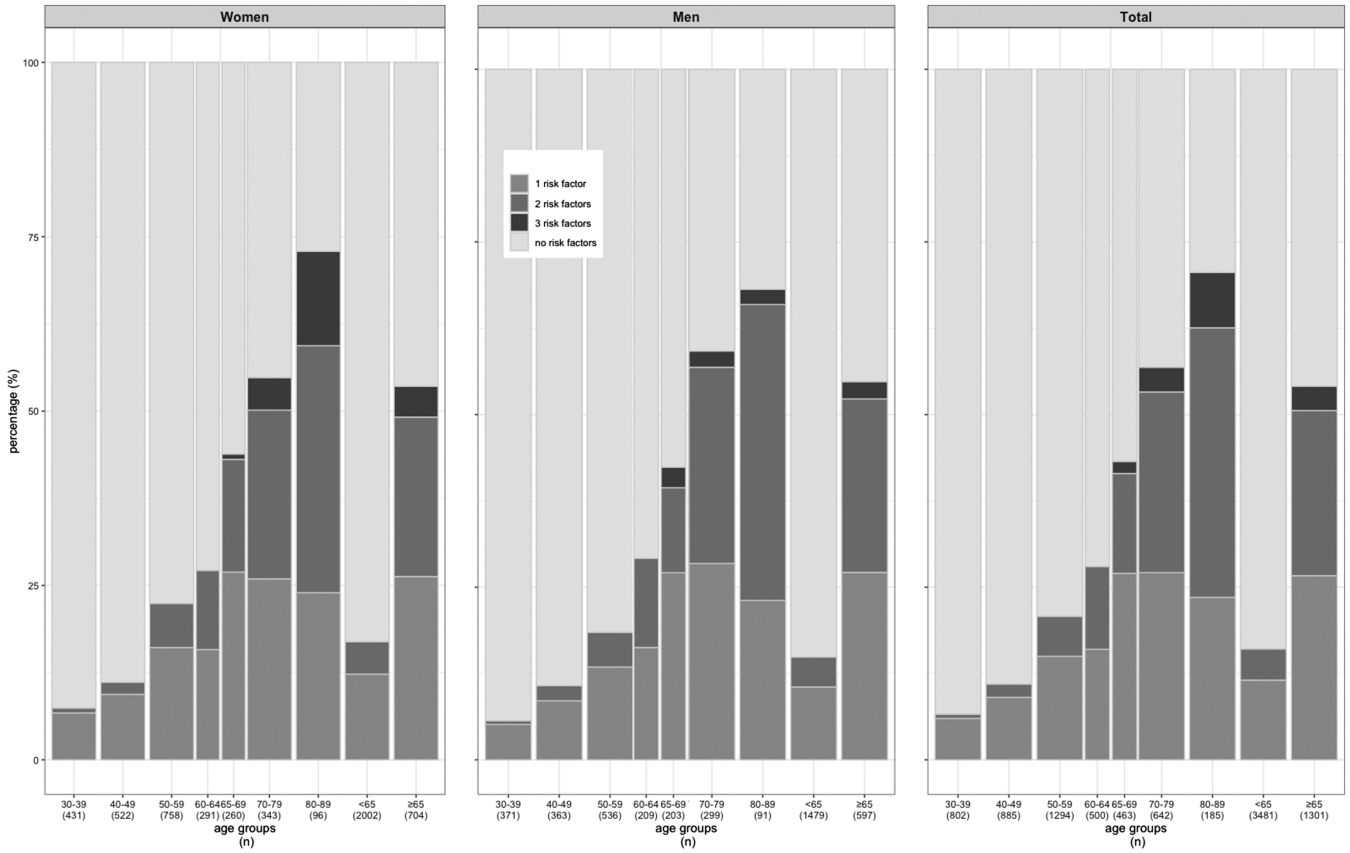

FIGURE 3 The number of prescribing (polypharmacy and use of PIM) and pharmacogenetic risk factors per participant, categorized by age and gender

The strength of our study is that we used interview-based medication data (including over-the-counter drugs), which is likely to better reflect actual medication use than secondary data. Interview-based medication data could, however, also have introduced recall bias in our study when asking for *as needed* used medication over the past year. We therefore mainly focused on regularly used medication. Another possible limitation is that the inclusion of the first 5000 participants of the Rhineland Study might represent a "healthier" population. However, this would most likely mean that we underestimated the risk for potential ADRs in the population. Additionally, we did not take drug-drug interactions into account, which could also have underestimated the risk of ADRs. Furthermore, we do not have information about the adherence to drug therapy and medication errors. The bidirectional association between nonadherence and ADRs makes this a challenging area of research that requires longitudinal data.[47] Lastly, our study was cross-sectional and we were not able to provide information on real ADRs. Given the high prevalence of risk factors for potential ADRs, further research should focus on detecting the actual burden of ADRs in clinical practice.

Our study shows that the individual risk for potential ADRs in the general population is high and suggests that there might be room for improvement of medication use in clinical practice. Especially in light of our aging population, increased awareness of the high prevalence of risk factors for ADRs is warranted.

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CONFLICT OF INTEREST

There are no competing interests to declare.

CONTRIBUTORS

All authors have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; all authors have been involved in drafting the manuscript or revising it critically for important intellectual content; all authors have given final approval of the version to be published. All authors participated sufficiently in the work to take public responsibility for appropriate portions of the content; and all authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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APPENDIX I: REGULAR AND *AS NEEDED* USE OF PGX DRUGS (BASED ON CPIC AND DPWG GUIDELINES)

Drug	Recommendation	Clinical effect
CYP2C9		
Flurbiprofen [a] (R = 0, PRN = 12)	**CPIC**: Initiate therapy with 25-50% of the lowest recommended starting dose for CYP2C9 poor metabolizers and initiating therapy with lowest recommended starting dose for CYP2C9 intermediate metabolizers with activity score of 1. **DPWG:** -	CYP2C9*2, CYP2C9*3: Increased risk of acute gastrointestinal bleeding [A1]
Ibuprofen [a] (R = 29, PRN = 1,133)		
Celecoxib [a] (R = 2, PRN = 7)		
Lornoxicam[a] (R = 0, PRN = 0)		
Meloxicam [a] (R = 4, PRN = 1)	**CPIC**: Alternative therapy for CYP2C9 poor metabolizers due to markedly prolonged half-life, and initiating therapy with 50% of the lowest recommended starting dose or choose an alternative therapy for CYP2C9 intermediate metabolizers with activity score of 1 is recommended. **DPWG:** -	
Piroxicam [a] (R = 1, PRN = 0)	**CPIC:** CYP2C9 poor metabolizers and intermediate metabolizers with activity score of 1 should choose an alternative therapy not metabolized by CYP2C9 or not significantly impacted by CYP2C9 genetic variants in vivo or choose an NSAID metabolized by CYP2C9 but with a shorter half-life.	
Tenoxicam[a] (R = 0, PRN = 0)	**CPIC:** CYP2C9 poor metabolizers and intermediate metabolizers with activity score of 1 should choose an alternative therapy not metabolized by CYP2C9 or not significantly impacted by CYP2C9 genetic variants in vivo or choose an NSAID metabolized by CYP2C9 but with a shorter half-life.	
Phenytoin [a,b] (R = 1, PRN = 0)	**CPIC:** Patients with the *CYP2C9* poor metabolizer phenotype or with a *CYP2C9* activity score of 1 may require reduced doses of phenytoin/fosphenytoin. **DPWG:** Use the standard starting dose of phenytoin and reduce the maintenance dose based on CYP2C9 genotype; monitor response and serum concentrations and be aware of ADEs.	CYP2C9*2, CYP2C9*3: Increase in the frequency of some side effects, such as cerebellar atrophy, gingival hypertrophy or acute cutaneous reactions [A2]
Siponimod [b] (R = 0, PRN = 0)	**CPIC:** -**DPWG:** Decreasing the dose for *CYP2C9* *1/*3, *2/*3 genotypes and to avoid siponimod for the *CYP2C9* *3/*3 genotype is recommended.	CYP2C9*2, CYP2C9*3: Increased risk of adverse events [A3]
Warfarin [a,b] (R = 0, PRN = 0)	**CPIC:** The recommendations for dosing are for adult and paediatric patients that are specific to continental ancestry, and are based on genotypes from *CYP2C9*, *VKORC1*, *CYP4F2* and rs12777823. **DPWG:** Reduce warfarin dose in CYP2C9 poor and intermediate metabolizers (PM and IM) and patients with CYP2C9*1/*3, *2/*3, *2/*2 or *3/*3 genotype.	CYP2C9*2 and CYP2C9*3: Greater risk of bleeding [A4]

(Continues)

Drug	Recommendation	Clinical effect
CYP2C19		
Lansoprazole [b] (R = 5, PRN = 1) Omeprazole [b] (R = 41, PRN = 46) Pantoprazole [b] (R = 227, PRN = 189)	**CPIC:** Increase the starting daily dose and to monitor efficacy in CYP2C19 ultrarapid metabolizer. For CYP2C19 rapid and normal metabolizers in the treatment of *H. pylori* infection and erosive esophagitis increasing the dose might be considered after initiation with the standard starting daily dose. The recommendations for intermediate and poor metabolizer for chronic therapy (>12 weeks) and efficacy achieved is to consider 50% reduction in daily dose. **DPWG:** -	CYP2C19*2, CYP2C19*3: Possible increase in adverse events including infections, electrolyte imbalances such as hypomagnesemia, kidney disease, and osteoporosis after long-term use. CYP2C19*17: Increased risk for therapeutic failure [A5]
Citalopram [a,b] (R = 54, PRN = 2) Escitalopram [a,b] (R = 41, PRN = 1)	**CPIC:** An alternative drug not predominantly metabolized by CYP2C19 for CYP2C19 ultrarapid metabolizers is recommended. For CYP2C19 poor metabolizers, consider a 50% reduction of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19. **DPWG:** For intermediate and poor metabolizers of CYP2C19 it is recommended not to exceed the in the DPWG document specified doses and for CYP2C19 ultrarapid metabolizer to avoid escitalopram.	PM: Increased risk of central nervous system effects (eg, insomnia, headache), gastrointestinal dysfunction, sexual dysfunction and arrhythmias caused by QT prolongation *CYP2C19*17* UM: Increased probability of failing therapy [A6]
Sertraline [a,b] (R = 19, PRN = 0)	**CPIC:** Consider a 50% reduction of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19 for CYP2C19 poor metabolizers. **DPWG:** Do not give doses exceeding 75 mg/day in patients with CYP2C19 poor metabolizer genotypes, and guide the dose by response and side effects and/or sertraline plasma concentration.	
Clomipramine [a] (R = 2, PRN = 0) Imipramine [a,b] (R = 0, PRN = 0) Trimipramine [a] (R = 16, PRN = 3) Doxepin [a] (R = 3, PRN = 1)	**CPIC:** Tricyclic antidepressants have comparable pharmacokinetic properties, it may be reasonable to apply the CPIC dosing guideline for amitriptyline and CYP2C19, CYP2D6 to other tricyclics, including imipramine. The CPIC dosing guideline update for amitriptyline recommends an alternative drug for CYP2D6 ultrarapid or poor metabolizers and CYP2C19 ultrarapid, rapid or poor metabolizers. If amitriptyline is warranted, consider a 50% dose reduction in CYP2D6 or CYP2C19 poor metabolizers. For CYP2D6 intermediate metabolizers, a 25% dose reduction should be considered. **DPWG:** Avoid clomipramine in CYP2C19 ultrarapid metabolizers for indication obsessive compulsive disorder or anxiety disorders. CYP2C19 poor metabolizers should receive 70% of the standard dose of imipramine, or imipramine should be avoided in these patients. Patients should be monitored	CYP2C19 *2/*2, *2/*3, *3/*3: Anticholinergic side effects and cardiotoxicity [A7]

Drug	Recommendation	Clinical effect
	for the effect and side effects or the plasma concentrations of imipramine and desipramine to set the maintenance dose.	
Amitriptyline [a] (R = 39, PRN = 8)	**CPIC:** An alternative drug for CYP2C19 ultrarapid, rapid or poor metabolizers is recommended. If amitriptyline is warranted, consider a 50% dose reduction in CYP2C19 poor metabolizers. **DPWG:** -	
Clopidogrel [a,b] (R = 44, PRN = 0)	**CPIC:** An alternative antiplatelet therapy (eg, prasugrel, ticagrelor) for CYP2C19 poor or intermediate metabolizers is recommended if there is no contraindication. **DPWG:** Avoid clopidogrel use in patients who are CYP2C19 poor metabolizers and are undergoing percutaneous coronary intervention, stroke or TIA. For CYP2C19 intermediate metabolizers who are undergoing percutaneous coronary intervention, stroke or TIA choose an alternative drug or double the dose to 150 mg/day (600 mg loading dose). No action is required for patients who are CYP2C19 ultra-rapid metabolizers.	CYP2C19 *2/*2, *2/*3, *3/*3: Increased risk of adverse CV outcomes [A8]
Voriconazole[a,b] (R = 0, PRN = 0)	**CPIC:** Selecting an alternative agent that is not dependent on CYP2C19 metabolism in adults who are CYP2C19 ultrarapid metabolizers, rapid metabolizers or poor metabolizers is recommended. In paediatric patients, an alternative agent should be used in patients who are ultrarapid metabolizers or poor metabolizers. In paediatric rapid metabolizers, therapy should be initiated at recommended standard case dosing, then therapeutic dosing monitoring should be used to titrate dose to therapeutic trough concentrations. **DPWG:** Patients who are CYP2C19 poor metabolizers should receive 50% of the standard dose, and CYP2C19 ultrarapid metabolizers should receive a 1.5 times higher initial dose. Monitor voriconazole plasma concentrations for CYP2C19 poor, intermediate and ultrarapid metabolizers.	CYP2C19 *2/*2, *2/*3, *3/*3: QTc prolongation (weak evidence) [A9]
CYP2D6		
Amitriptyline[a,b] (R = 39, PRN = 8)	**CPIC:** An alternative drug for CYP2D6 ultrarapid or poor metabolizers is recommended. If amitriptyline is warranted, consider a 50% dose reduction in CYP2D6 poor metabolizers. **DPWG:** Decreasing the dose for CYP2D6 intermediate and CYP2D6 poor metabolizers and increasing the dose or using an alternative drug for CYP2D6 ultra-rapid metabolizers is recommended.	CYP2D6 *3-*8, *11-*16, *18-*21, *38, *40, *42: Increased risk of adverse events, eg, cardiotoxicity [A6]
Clomipramine[a,b] (R = 2, PRN = 0)	**CPIC:** Tricyclic antidepressants have comparable pharmacokinetic properties,	
Doxepin[a,b] (R = 3, PRN = 1)		

(Continues)

Drug	Recommendation	Clinical effect
Imipramine[a,b] (R = 0, PRN = 0)	it may be reasonable to apply the CPIC dosing guideline for amitriptyline and CYP2C19, CYP2D6 to other tricyclics including clomipramine. The CPIC dosing guideline update for amitriptyline recommends an alternative drug for CYP2D6 ultrarapid or poor metabolizers and CYP2C19 ultrarapid, rapid or poor metabolizers. If amitriptyline is warranted, consider a 50% dose reduction in CYP2D6 or CYP2C19 poor metabolizers. For CYP2D6 intermediate metabolizers, a 25% dose reduction should be considered. **DPWG:** Doxepin: Dose changes and to monitor the effect and side effects or the plasma concentrations to set the maintenance dose for CYP2D6 poor, intermediate and ultrarapid metabolizers or to avoid doxepin in UM is recommended. Imipramine: CYP2D6 poor metabolizers should receive 30% of the standard dose of imipramine, CYP2D6 intermediate metabolizers should receive 70% of the standard dose and CYP2D6 ultra-rapid metabolizers should receive 1.7 times the standard dose. Patients should be monitored for the effect and side effects or the plasma concentrations of imipramine and desipramine to set the maintenance dose.	
Nortriptyline [a,b] (R = 0, PRN = 0)	**CPIC:** The CPIC dosing guideline update for nortriptyline recommends a 25% dose reduction for CYP2D6 intermediate metabolizers. For CYP2D6 ultrarapid or poor metabolizers, an alternative drug should be considered. If nortriptyline is warranted, consider a 50% dose reduction in CYP2D6 poor metabolizers. **DPWG:** A dose reduction for CYP2D6 poor or intermediate metabolizer patients is recommended. For CYP2D6 ultrarapid metabolizers, select an alternative drug or use 1.7 times the standard dose. Monitoring of nortriptyline and 10-hydroxynortriptyline plasma concentrations is recommended.	
Trimipramine [a] (R = 16, PRN = 3)	**CPIC:** Tricyclic antidepressants have comparable pharmacokinetic properties, it may be reasonable to apply the CPIC dosing guideline for amitriptyline and CYP2C19, CYP2D6 to other tricyclics including trimipramine. The CPIC dosing guideline update for amitriptyline recommends an alternative drug for CYP2D6 ultrarapid or poor metabolizers and CYP2C19 ultrarapid, rapid or poor metabolizers. If amitriptyline is warranted, consider a 50% dose reduction in CYP2D6 or CYP2C19 poor metabolizers. For CYP2D6 intermediate metabolizers, a	

Drug	Recommendation	Clinical effect
	25% dose reduction should be considered. **DPWG:** -	
Desipramine[a] (R = 0, PRN = 0)	**CPIC:** Tricyclic antidepressants have comparable pharmacokinetic properties, it may be reasonable to apply the CPIC dosing guideline for amitriptyline/nortriptyline and CYP2C19, CYP2D6 to other tricyclics, including desipramine. The CPIC dosing guideline update for nortriptyline recommends a 25% dose reduction for CYP2D6 intermediate metabolizers. For CYP2D6 ultrarapid or poor metabolizers, an alternative drug should be considered. If nortriptyline is warranted, consider a 50% dose reduction in CYP2D6 poor metabolizers. **DPWG:** -	
Fluvoxamine [a] (R = 1, PRN = 0)	**CPIC:** Consider a 25-50% reduction of recommended starting dose and titrate to response or use an alternative drug not metabolized by CYP2D6 for CYP2D6 poor metabolizers. **DPWG:** -	CYP2D6 **3-*8, *11-*16, *18-*21, *38, *40, *42*: Increased risk of central nervous system effects (eg, insomnia, headache), gastrointestinal dysfunction, sexual dysfunction and arrhythmias caused by QT prolongation [A7]
Paroxetine [a,b] (R = 11, PRN = 0)	**CPIC:** An alternative drug not predominantly metabolized by CYP2D6 for CYP2D6 ultrarapid metabolizers and for CYP2D6 poor metabolizers is recommended. For CYP2D6 poor metabolizers, if paroxetine use is warranted, consider a 50% reduction of recommended starting dose and titrate to response. **DPWG:** Select an alternative drug rather than paroxetine for CYP2D6 ultrarapid metabolizer patients.	
Aripiprazole [b] (R = 4, PRN = 0)	**CPIC:** - **DPWG:** Reducing maximum dose of aripiprazole for patients carrying poor metabolizer alleles of CYP2D6 is recommended.	CYP2D6 **3-*8, *11-*16, *18-*21, *38, *40, *42*: Neuroleptic malignant syndrome, and tardive dyskinesia [A3]
Brexpiprazole[b] (R = 0, PRN = 0)	**CPIC:** - **DPWG:** Use half of the standard dose of brexpiprazole for patients carrying poor metabolizer alleles of CYP2D6.	CYP2D6 **3-*8, *11-*16, *18-*21, *38, *40, *42*: Increased risk of side effects [A3]
Atomoxetine[a,b] (R = 1, PRN = 0)	**CPIC:** For CYP2D6 ultrarapid, normal, intermediate and poor metabolizers, which includes guidance for plasma drug concentration testing, as a means to estimate atomoxetine exposure, if no clinical response and in the absence of adverse events after 2 weeks of therapy. **DPWG:** For CYP2D6 ultrarapid metabolizers, to be alert to reduced efficacy of atomoxetine or select an alternative drug as a precaution. Be alert to ADEs in CYP2D6 poor metabolizers.	CYP2D6 *3/*4, *4/*4, *5/*5, *5/*6: Dry mouth, blurred vision, sleep disturbances, decreased weight or appetite, constipation, depression, tremor, feeling jittery, excoriation, dry eye or conjunctivitis, syncope, urinary retention, sexual dysfunction, hyperhidrosis, peripheral coldness, and elevated blood pressure [A10]
Codeine[a,b] (R = 1, PRN = 6)	**CPIC:** Alternate analgesics are recommended for CYP2D6 ultrarapid and poor metabolizers. A label recommended	CYP2D6 *4/*4, *4/*5, *5/*5, *4/*6: Little therapeutic effect

(Continues)

Drug	Recommendation	Clinical effect
	age- or weight-specific codeine dose is warranted for CYP2D6 extensive and intermediate metabolizers. **DPWG:** There are individual recommendations for cough or pain for CYP2D6 poor, intermediate and ultrarapid metabolizers. In addition, for ultrarapid metabolizers, higher or lower doses and additional risk factors are taken into consideration.	CYP2D6 *1/*1xN, *1/*2xN: Risk of morphine toxicity (drowsiness, lightheadedness, dizziness, sedation, shortness of breath, nausea, vomiting, and sweating) [A11]
Eliglustat [b] (R = 0, PRN = 0)	**CPIC:** - **DPWG:** Use an alternative in CYP2D6 ultrarapid metabolizers. For CYP2D6 poor metabolizers in combination with CYP3A inhibitors and strong inducers, the guideline recommends choosing an alternative if possible. For intermediate metabolizers recommendations are provided for co-medication with CYP2D6 and/or CYP3A inhibitors and CYP3A inducers.	CYP2D6 *4/*4, *4/*5, *5/*5, *4/*6: Increased risk of side effects such as (small, dose-dependent) elongation of the QT interval [A3]
Flecainide [b] (R = 15, PRN = 1)	**CPIC:** - **DPWG:** Reduce flecainide dose by 50% for CYP2D6 poor metabolizers and record an ECG and monitor the plasma concentration. Reduce flecainide dose to 75% of the standard dose for CYP2D6 intermediate metabolizers with indications other than diagnosis of Brugada syndrome and record an ECG and monitor the plasma concentration.	CYP2D6 *4/*4, *4/*5, *5/*5, *4/*6: Increased risk of side effects. [A3]
Haloperidol [b] (R = 0, PRN = 0)	**CPIC:** - **DPWG:** Reduce haloperidol dose by 50% or select an alternative drug for CYP2D6 poor metabolizer genotype patients.	CYP2D6 *4/*4, *4/*5, *5/*5, *4/*6: Extrapyramidal adverse reactions [A12]
Metoprolol [b] (R = 111, PRN = 1)	**CPIC:** - **DPWG:** For CYP2D6 poor and intermediate metabolizer patients, if a gradual reduction in heart rate is desired, or in the event of symptomatic bradycardia, increase the dose in smaller steps and/or prescribe no more than 25% or 50% of the standard dose, respectively. For CYP2D6 ultra metabolizers, use the maximum dose for the relevant indication as a target dose, and if the effectiveness is still insufficient: Increase the dose based on effectiveness and side effects to 2.5 times the standard dose or select an alternative drug.	CYP2D6 *4/*4, *4/*5, *5/*5, *4/*6: Greater reductions in heart rate, diastolic blood pressure and mean arterial pressure [A13]
Ondansetron [a] (R = 0, PRN = 0) Tropisetron [a] (R = 0, PRN = 0)	**CPIC:** Select an alternate drug for CYP2D6 ultrarapid metabolizers. It is recommended that the alternate drug not be predominantly metabolized by CYP2D6 (eg, Granisetron). **DPWG**: -	CYP2D6 *1/*1xN, *1/*2xN: Decreased antiemetic effect [A14]
Pimozide [b] (R = 0, PRN = 0)	**CPIC:** - **DPWG:** Patients who are CYP2D6 intermediate metabolizers should be given no more than 80% of the standard maximum dose of pimozide while	CYP2D6 *4/*4, *4/*5, *5/*5, *4/*6: The risk of QT-prolongation, and thereby also the risk of torsade de points, is theoretically increased [A3]

Drug	Recommendation	Clinical effect
	patients who are CYP2D6 poor metabolizers should be given no more than 50% of the standard maximum dose.	
Propafenone [b] (R = 6, PRN = 1)	**CPIC:** - **DPWG:** Reduce the dose of propafenone by 70% for CYP2D6 poor metabolizers, and monitor propafenone plasma concentrations or use an alternative drug for CYP2D6 intermediate and ultrarapid metabolizers.	CYP2D6 *4/*4, *4/*5, *5/*5, *4/*6: Arrhythmias, bradycardia and bronchospasm [A15]
Risperidone [b] (R = 1, PRN = 0)	**CPIC:** - **DPWG:** Decrease the dose for CYP2D6 poor metabolizers and using an alternative drug or titrate the dose according to the maximum dose for the active metabolite for CYP2D6 ultrarapid metabolizers.	CYP2D6 *4/*4, *4/*5, *5/*5, *4/*6: Weight gain and prolactin [A16]
Tamoxifen [a,b] (R = 24, PRN = 0)	**CPIC:** The CPIC dosing guideline for tamoxifen recommends the use of alternative hormonal therapy such as an aromatase inhibitor for postmenopausal women or aromatase inhibitor along with ovarian function suppression in premenopausal women for CYP2D6 poor metabolizers, if aromatase inhibitor use is not contraindicated. For CYP2D6 intermediate metabolizers and CYP2D6 allele combinations resulting in an activity score (AS) of 1 the recommendation is to consider the recommendations stated for the CYP2D6 poor metabolizer. If aromatase inhibitor use is contraindicated, consideration should be given to use a higher but FDA approved tamoxifen dose for CYP2D6 intermediate metabolizers and CYP2D6 allele combinations resulting in an AS of 1. For poor metabolizers, higher dose tamoxifen (40 mg/day) increases but does not normalize endoxifen concentrations and can be considered if there are contraindications to aromatase inhibitor therapy. **DPWG:** For CYP2D6 poor and intermediate metabolizers, consider an alternative medication or a dose increase. For intermediate metabolizers, avoid concomitant CYP2D6 inhibitor use.	CYP2D6 *3/*4,*4/*4, *5/*5, *5/*6: Higher risk of disease recurrence [A17]
Tramadol [b] (R = 3, PRN = 9)	**CPIC:** - **DPWG:** Be alert to a reduced efficacy of tramadol in CYP2D6 intermediate or poor metabolizers. If tramadol is not effective in these patients, try a dose increase or select an alternative to tramadol (not codeine) and be alert for symptoms of insufficient pain relief. For CYP2D6 ultrarapid metabolizers, use an alternative to tramadol (not codeine) or use 40% of the standard dose and be alert to side effects.	CYP2D6 *1/*1xN, *1/*2xN: Nausea, vomiting, constipation, respiratory depression, confusion, urinary retention *CYP2D6 *3/*4,*4/*4, *5/*5, *5/*6*: Insufficient pain relief. [A18]

(Continues)

Drug	Recommendation	Clinical effect
Venlafaxine [b] (R = 55, PRN = 0)	**CPIC:** - **DPWG:** For CYP2D6 poor and intermediate metabolizers, select an alternative to venlafaxine or reduce the dose and monitor patient's plasma metabolite level. For CYP2D6 ultrarapid metabolizers, increase dose to 150% of the normal dose or select an alternative to venlafaxine.	*CYP2D6 *3/*4,*4/*4, *5/*5, *5/*6*: Increased risk of gastrointestinal side effects, such as vomiting and diarrhoea, and cardiovascular side effects, such as hypertension, tachycardia and prolonged QTc interval [A19]
Zuclopenthixol [b] (R = 0, PRN = 0)	**CPIC:** - **DPWG:** For CYP2D6 poor and intermediate metabolizers, reduce zuclopenthixol dose or select an alternative drug that is not metabolized by CYP2D6. For ultrarapid metabolizers, be alert to low zuclopenthixol plasma concentrations and, if necessary, increase the dose or select an alternative drug.	CYP2D6 *4/*4, *4/*5, *5/*5, *4/*6: Increased risk of adverse effects [A3]
SLCO1B1		
Atorvastatin [b] (R = 270, PRN = 2)	**CPIC:** - **DPWG:** Choose an alternative for patients with the SLCO1B1 521 CC or TC (rs4149056) genotype and with additional significant risk factors for statin-induced myopathy. For patients without additional significant risk factors for statin-induced myopathy, advise the patients to contact their doctor in the event of muscle symptoms.	SLCO1B1*5: Myopathy [A20]
Simvastatin [a,b] (R = 215, PRN = 3)	**CPIC:** The FDA recommends against 80 mg daily simvastatin dosage. In patients with the C allele at SLCO1B1 **rs4149056**, there are modest increases in myopathy risk even at lower simvastatin doses (40 mg daily); if optimal efficacy is not achieved with a lower dose, alternate agents should be considered. **DPWG:** Choose an alternative for patients with the SLCO1B1 521 CC or TC (rs4149056) genotype and consider any additional risk factors for statin-induced myopathy. If an alternative is not an option for patients with the 521 TC genotype, avoid simvastatin doses exceeding 40 mg/day and advise the patient to contact their doctor in the event of muscle symptoms.	SLCO1B1*5: Myopathy [A20]
VKORC1		
Acenocoumarol [b] (R = 0, PRN = 0)	**CPIC:** - **DPWG:** Patients with the VKORC1-1639 (**rs9923231**) AA genotype should be given 50% of the standard initial dose of acenocoumarol and undergo more frequent INR monitoring. There are no recommendations for patients with the VKORC1-1639 AG genotype.	VKORC1-1639G>A: Bleeding [A21]
Phenprocoumon [b] (R = 39, PRN = 1)	**CPIC:** - **DPWG:** Patients with the VKORC1-1639 (rs9923231) AA genotype are recommended to be given 50% of the standard initial dose of phenprocoumon	VKORC1-C1173T: Bleeding [A22]

Drug	Recommendation	Clinical effect
	and more frequent monitoring of INR. The genotype-specific initial dose and maintenance dose can be calculated using an algorithm. There is no recommendation for patients with the VKORC1-1639 AG genotype.	
Warfarin [b] (R = 0, PRN = 0)	**CPIC:** - **DPWG:** Patients with the VKORC1-1639 (rs9923231) AA genotype should be given 60% of the standard initial dose of warfarin. The genotype-specific initial dose and maintenance dose can be calculated using an algorithm. There are no recommendations for patients with the VKORC1-1639 AG genotype.	VKORC1-1639G>A: Greater risk of bleeding [A23]

Abbreviations: ADE, adverse drug event; AS, activity score; CPIC, Clinical Pharmacogenetics Implementation Consortium; CV, cardiovascular; CYP, Cytochromes P450; DPWG, Dutch Pharmacogenetics Working Group; FDA, Food and Drug Administration; IM, intermediate metabolizer; INR, International Normalized Ratio; NSAID, non-steroidal anti-inflammatory drugs; PM, poor metabolizer; PRN, pro re nata; R, regularly; TIA, Transient Ischemic Attack; UM, ultrarapid metabolizer.

a. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines
b. Dutch Pharmacogenetics Working Group (DPWG) guidelines

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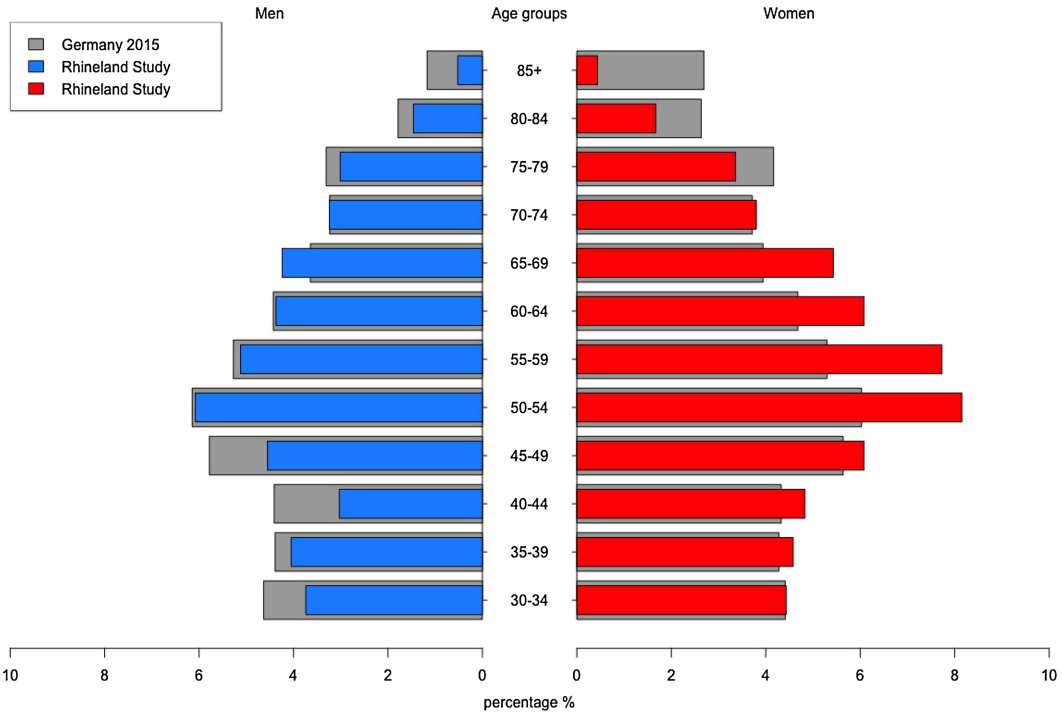
APPENDIX II: AGE PYRAMID RHINELAND STUDY POPULATION COMPARED TO THE GERMAN POPULATION IN 2015[38]



APPENDIX III: TOP 15 MOST *AS NEEDED* USED DRUG CLASSES (IF USED 10 DAYS OR MORE DURING THE LAST YEAR) FOR WOMEN AND MEN

	Women (n = 2706)				Men (n = 2076)			
	ATC	Name	Users, n (%)	Number of days used during last year: 10-50 days, >50	ATC	Name	Users, n (%)	Number of days used during last year: 10-50 days, >50
1	M01	Anti-inflammatory and antirheumatic products	877, 32.4%	82%, 18%	M01	Anti-inflammatory and antirheumatic products	401, 19.3%	86%, 14%
2	N02	Analgesics	428, 15.8%	82%, 18%	N02	Analgesics	201, 9.7%	84%, 16%
3	R01	Nasal preparations	309, 11.4%	79%, 21%	R01	Nasal preparations	185, 8.9%	74%, 26%
4	A02	Drugs for acid-related disorders	181, 6.7%	61%, 39%	R06	Antihistamines for systemic use	148, 8.5%	66%, 34%
5	R06	Antihistamines for systemic use	177, 6.5%	63%, 37%	A02	Drugs for acid-related disorders	136, 6.6%	60%, 40%
6	R05	Cough and cold preparations	165, 6.1%	89%, 11%	R05	Cough and cold preparations	106, 5.1%	95%, 5%
7	S01	Ophthalmologicals	116, 4.3%	43%, 57%	R03	Drugs for obstructive airway diseases	73, 3.5%	56%, 44%
8	R03	Drugs for obstructive airway diseases	111, 4.1%	60%, 40%	N05	Psycholeptics	60, 2.9%	55%, 45%
9	A03	Drugs for functional gastrointestinal disorders	102, 3.8%	76%, 24%	S01	Ophthalmologicals	57, 2.7%	70%, 30%
10	N05	Psycholeptics	95, 3.5%	63%, 37%	D01	Antifungals for dermatological use	57, 2.7%	70%, 30%
11	M02	Topical products for joint and muscular pain	81, 3.0%	73%, 27%	M02	Topical products for joint and muscular pain	41, 2.0%	80%, 20%
12	A11	Vitamins	67, 2.5%	49%, 51%	D07	Corticosteroids, dermatologicals	37, 1.8%	70%, 30%
13	R02	Throat preparations	58, 2.1%	88%, 12%	R02	Throat preparations	27, 1.3%	96%, 4%
14	D07	Corticosteroids, dermatological preparations	50, 1.8%	72%, 28%	A03	Drugs for functional gastrointestinal disorders	22, 1.1%	68%, 32%
15	A07	Antidiarrheals	35, 1.3%	71%, 29%	A07	Antidiarrheals	16, 0.8%	63%, 37%

ATC, Anatomical Therapeutic Chemical.

APPENDIX IV: DRUGS LISTED ON THE PRISCUS LIST WITH TOTAL NUMBER OF USERS AGED 65 YEARS OR OLDER

Analgesics, anti-inflammatory drugs (R = 3, PRN = 11)	**Imipramine (R = 0, PRN = 0)**	**Sedatives, hypnotic drugs (R = 13, PRN = 45)**
Indomethacin (R = 0, PRN = 1)	Clomipramine (R = 0, PRN = 0)	Chlordiazepoxide (R = 0, PRN = 0)
Acemetacin (R = 0, PRN = 0)	Maprotiline (R = 1, PRN = 0)	Diazepam (R = 0, PRN = 3)
Ketoprofen (R = 0, PRN = 0)	Trimipramine (R = 3, PRN = 2)	Flurazepam (R = 0, PRN = 0)
Piroxicam (R = 0, PRN = 0)	Fluoxetine (R = 6, PRN = 0)	Dipotassium clorazepate (R = 0, PRN = 0)
Meloxicam (R = 2, PRN = 0)	Tranylcypromine (R = 0, PRN = 0)	Bromazepam (R = 2, PRN = 6)
Phenylbutazone (R = 0, PRN = 0)	**Antiemetic drugs (R = 0, PRN = 2)**	Prazepam (R = 0, PRN = 0)
Etoricoxib (R = 1, PRN = 10)	Dimenhydrinate (R = 0, PRN = 2)	Clobazam (R = 1, PRN = 0)
Pethidine (R = 0, PRN = 0)	**Antihypertensive agents and other cardiovascular drugs (R = 9, PRN = 0)**	Nitrazepam (R = 0, PRN = 0)
Antiarrhythmic drugs (R = 14, PRN = 1)	Clonidine (R = 1, PRN = 0)	Flunitrazepam (R = 0, PRN = 1)
Quinidine (R = 0, PRN = 0)	Doxazosin (R = 7, PRN = 0)	Medazepam (R = 0, PRN = 0)
Flecainide (R = 13, PRN = 1)	Prazosin (R = 0, PRN = 0)	Alprazolam (R = 0, PRN = 1)
Sotalol (R = 0, PRN = 0)	Terazosin (as an antihypertensive agent) (R = 0, PRN = 0)	Temazepam (R = 0, PRN = 0)
Digoxin (R = 0, PRN = 0)	Methyldopa (R = 0, PRN = 0)	Triazolam (R = 0, PRN = 0)
Acetyldigoxin (R = 1, PRN = 0)	Reserpine (R = 0, PRN = 0)	Lorazepam (>2 mg/d) (R = 0, PRN = 0)
Metildigoxin (R = 0, PRN = 0)	Nifedipine (R = 0, PRN = 0)	Oxazepam (>60 mg/d) (R = 0, PRN = 0)
Antibiotics (R = 3, PRN = 1)	Thioridazine (R = 0, PRN = 0)	Lormetazepam (>0.5 mg/d) (R = 0, PRN = 2)
Nitrofurantoin (R = 3, PRN = 1)	Fluphenazine (R = 0, PRN = 0)	Brotizolam (>0.125 mg/d) (R = 0, PRN = 0)
Anticholinergic drugs (R = 14, PRN = 5)	Levomepromazine (R = 0, PRN = 0)	Zolpidem (>5 mg/d) (R = 1, PRN = 11)
Hydroxyzine (R = 0, PRN = 1)	Perphenazine (R = 0, PRN = 0)	Zopiclone (>3.75 mg/d) (R = 4, PRN = 12)
Clemastine (R = 0, PRN = 0)	Haloperidol (>2 mg) (R = 0, PRN = 0)	Zaleplon (>5 mg/d) (R = 0, PRN = 0)
Dimetindene (R = 0, PRN = 2)	Olanzapine (R = 1, PRN = **0**)	Doxylamine (R = 3, PRN = 5)
Chlorpheniramine (R = 0, PRN = 1)	Clozapine (R = 0, PRN = 0)	Diphenhydramine (R = 2, PRN = 4)
Triprolidine (R = 0, PRN = 0)	**Ergotamine and its derivatives (R = 0, PRN = 0)**	Chloral hydrate (R = 0, PRN = 0)
Oxybutynin (R = 3, PRN = 0)	Ergotamine (R = 0, PRN = 0)	**Antidementia drugs, vasodilators, circulation-promoting agents (R = 3, PRN = 0)**
Tolterodine (R = 0, PRN = 0)	Dihydroergocryptine (R = 0, PRN = 0)	Pentoxifylline (R = 0, PRN = 0)

Analgesics, anti-inflammatory drugs (R = 3, PRN = 11)	Imipramine (R = 0, PRN = 0)	Sedatives, hypnotic drugs (R = 13, PRN = 45)
Solifenacin (R = 11, PRN = 1)	Dihydroergotoxin (R = 0, PRN = 0)	Naftidrofuryl (R = 2, PRN = 0)
Inhibitors of platelet aggregation (R = 0, PRN = 0)	Laxatives (R = 0, PRN = 0)	Nicergoline (R = 0, PRN = 0)
Ticlopidine (R = 0, PRN = 0)	Viscous paraffin (R = 0, PRN = 0)	Piracetam (R = 1, PRN = 0)
Prasugrel (R = 0, PRN = 0)	Muscle relaxants (R = 0, PRN = 0)	Antiepileptic drugs (R = 0, PRN = 0)
Antidepressants (R = 29, PRN = 3)	Baclofen (R = 0, PRN = 0)	Phenobarbital (R = 0, PRN = 0)
Amitriptyline (R = 18, PRN = 0)	Tetrazepam (R = 0, PRN = 0)	
Doxepin (R = 1, PRN = 1)		

R, regular use; PRN, pro re nata.

APPENDIX V: RISK FACTORS AFTER INCLUDING BOTH REGULARLY AND *AS NEEDED* USED DRUGS

TABLE Va Use of PGX drugs, when including both regularly and *as needed* used drugs

		Women	Men	Total
Use of at least one drug PGX drug when including both regularly and as needed used drugs	n	1234	802	2036
	%	45.6%	38.6%	42.6%
	95% CI	(43.7, 47.5)	(36.5, 40.7)	(41.2, 44.0)

TABLE Vb Prevalence of participants with at least one risk factor when including both regularly and as needed used drugs

		<65 years			≥65 years		
		Women	**Men**	**Total**	**Women**	**Men**	**Total**
Regularly used medication							
At least one risk factor	n	339	220	559	377	327	704
	%	16.9%	14.9%	16.0%	53.6%	54.8%	54.1%
	95% CI	(15.3, 18.6)	(13.1, 16.7)	(14.8, 17.3)	(49.9, 57.2)	(50.8, 58.8)	(51.4, 56.8)
Regularly and *as needed* used medication							
At least one risk factor	n	909	513	1,422	450	365	815
	%	45.4%	34.7%	40.9%	63.9%	61.1%	62.6%
	95% CI	(43.2, 47.6)	(32.3, 37.1)	(39.2, 42.5)	(60.4, 67.5)	(57.2, 65.0)	(60.0, 65.3)