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Trends in use of antipsychotics in Germany 2014–2024: a nationwide population-based study

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Abstract

Background Antipsychotic medication (APM) use in children and adolescents in Germany increased over decades. However, contemporary data across all age groups is lacking. We aimed to analyze outpatient APM use across all age groups in Germany between 2014 and 2024.

Methods We analyzed anonymized Statutory Health (SH) Insurance claims data (approximately 87% of the German population) from the German Institute for Drug Use Evaluation (DAPI), selected the Anatomical Therapeutic Chemical (ATC) code N05A (antipsychotics) except lithium, analyzed defined daily doses per 1,000 SH-insured persons per day (DID), stratified by age group, type of APM [first-generation antipsychotic (FGA) vs. second-generation antipsychotic (SGA)] and performed linear regression analyses.

Results Overall APM use increased from 2014 to 2024 by 2% (11.44 to 11.71 DID, $p = 0.304$). While the FGA use fell by 29% (3.96 to 2.82, $p < 0.001$), SGA use rose by 19% (7.48 to 8.89, $p < 0.001$). The largest increases occurred in the age groups 15–19 (+ 32%), 20–24 (+ 29%), 60–64 (+ 20%), 65–69 (+ 34%) and 70–74 years (+ 22%). During the study period, use of aripiprazole (+ 106%), olanzapine (+ 25%), and quetiapine (+ 19%) rose. However, risperidone and clozapine decreased (-2% and − 11%, respectively). In 2024, APM use peaked at age 60–64, dropped in 65–74 and rose again from 75, reaching a maximum in those 90 + years, while the general practitioners (GPs) APM prescriptions proportion rose with patient´s age

Conclusions Antipsychotic medication use in Germany stayed mainly stable during the study period but showed considerable age-specific shifts, including increasing APM use in ages 15 to 24, 60 to 74, and a very high use of APM in patients 90+. Clozapine use has declined in most age groups, which may indicate continued underutilization despite strong evidence supporting its effectiveness in treatment resistant schizophrenia. These findings highlight the need for age-specific monitoring of prescribing behaviour.

Keywords Antipsychotic agents, Drug utilization, Mental disorders, Longitudinal studies, Pharmacoepidemiology

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Background

Mental disorders are among the diseases with the greatest burden worldwide. In 2021, they accounted for approximately 1.1 billion prevalent cases and 444 million incident cases globally. Between 2010 and 2021, the global prevalence of mental disorders increased by 22.8% while incidence rose by 36.7% highlighting a growing public health challenge [1, 2].

Use of antipsychotic medication (APM) among children and adolescents in Germany has continued to increase during the period between 2011 and 2020 [3] and a high rate of APM use among the older adults has been reported [4].

In many countries, the prescribing pattern of APM has shifted. While prescribing rates of first-generation antipsychotics (FGA) have declined [5], the use of atypical or second-generation antipsychotics (SGA) increased [4].

This might be due to differences in the side effect profile, having the SGA a decreased risk of extrapyramidal side effects as compared to FGA [4, 6]. However, SGA are associated with cardiometabolic side effects (e.g., weight gain, obesity, hypertension, and lipid and glucose abnormalities) that have been of concern in recent years, particularly in children and adolescents. The use of SGA in naïve young patients has been associated with a significant age-inappropriate weight gain in the four APMs studied: aripiprazole, olanzapine, quetiapine and risperidone [7]. Moreover, a high body mass index (BMI) in childhood is related to an increased risk of obesity, metabolic syndrome, cardiovascular morbidity and malignancy in later adulthood [8–9]. Contemporary data regarding the use of APM across all age groups in Germany is lacking, however. We, therefore, aimed to analyze outpatient APM use across all age groups and by type of prescribers in Germany between 2014 and 2024.

Methods

We used data from the German Institute for Drug Use Evaluation (Deutsches Arzneiprüfungsinstitut e.V., DAPI, http://www.dapi.de).

In Germany, healthcare is mandatory and splits between statutory health insurance (SHI, 87% of the population) and private health insurance, available to high earners, civil servants, and self-employed. When a SHI prescription is filled at a community pharmacy, the pharmacy submits the claim to one of the data processing centres, which handles billing and reimbursement. The data processing centre anonymizes and aggregates the data, which is then made available to the DAPI database. SHI prescriptions issued directly to physicians for use in their practices (so-called consultation supplies) were not analysed in our study because it was not possible to stratify these prescriptions by age, therefore only individually issued prescriptions were considered.

The database contains anonymized prescription claims data from more than 80% (until June 2019) and more than 95% (from July 2019 onwards) of Germany's community pharmacies at the expense of SHI funds. Data were extrapolated by regional factors to represent 100% of the population insured by the. The database did not include prescriptions for privately insured patients or inpatient use neither information on indication, treatment duration or prescribed doses. The data was linked to a database containing information on the product´s details, via a unique identification number called "Pharmazentralnummer" used for pharmaceutical products in Germany.

We applied the Anatomical Therapeutic Chemical (ATC) classification system for APM identified under the code N05A (except lithium N05AN01), and analyzed the use of APM measured in defined daily doses (DDD) per 1,000 SHI-insured persons per day (DID) for each year of the study period (2014 to 2024).

The DDD is defined by the World Health Organization as the assumed average maintenance dose per day of a drug for its main indication in adults [10]. Therefore, it does not necessarily correspond to the prescribed daily dose for individual patients. Because DDDs are based on adult dosing for the main indication, they may not accurately reflect drug consumption in paediatric populations, for other than the main indication, or for off-label use. Therefore, DDD-based estimates should be interpreted as standardized measures of drug consumption rather than accurate representations of dosing for individual patients.

To select the DDD of each APM, we used the official version of the German ATC classification system with DDD published by the Federal Institute for Drugs and Medical Devices [11].

We analyzed the use of APM in three progressively specific levels, narrowing the focus of the analysis from all APM initially to the type of APM (FGA vs. SGA) and finally to individual APM substance (ATC level 5), limited to the top four APM based on 2024 DID and clozapine. Within each level, each analysis was done with and without age stratification to understand how age might influence prescribing patterns. We divided the age groups into 5-year intervals with the exception of the age groups 0–14 years and 90 + years.

We performed a series of linear regression analyses to explore associations between calendar year and APM use. For these analyses, a linear relationship was assumed between time and APM use. We ran separate regressions at the different levels without age stratification. The statistical significance was assessed using a t-test. Statistical significance was determined at a threshold of $p < 0.05$. Corresponding P-values and regression slopes

(= estimate in DID per year) with 95% confidence intervals were calculated.

In addition, we analyzed the 2024 data across three types of prescribers: general practitioners (including paediatricians), neurologists/psychiatrists, and all other physician types. We analyzed APM, FGA, SGA and the 5 most prescribed APM substances in the 90 + age group. We also compared the change in the percentage of DID prescriptions issued by general practitioners in 2024 between the age groups with the lowest and highest proportions of such prescriptions.

All analyses were conducted using R version 4.4.1.

Ethical approval

Ethical Committee approval was not required for this study, as it was conducted using fully anonymized statutory health insurance claims data in accordance with German data protection regulations.

Results

Overall use of APM

From 2014 to 2024, the overarching APM use in Germany showed a statistically non-significant increase of 2% (11.44 to 11.71 DID, $p = 0.304$). While the use of SGA increased significantly by 19%, (7.48 to 8.89 DID, $p < 0.001$), the use of FGA decreased significantly by 29%, (3.96 to 2.82 DID, $p < 0.001$). For details see Fig. 1; Table 1.

Use of APM in different age groups

The age groups in which DID increased the most were: '65 to 69' (34%, 12.49 to 16.72 DID), '15 to 19' (32%, 1.62 to 2.13) '20 to 24' (29%, 3.88 to 4.99), '70 to 74' (22%, 11.43 to 13.92), and the '60 to 64' (20%, 15.83 to 18.96) years old (Table 2).

The highest increase in SGA was in the age group '65 to 69' (66%, 7.33 to 12.17 DID) followed by the age group '60 to 64' with an 49% increase (9.43 to 14.10) and the age group '70 to 74' (45%, 6.86 to 9.96). See Table 2; Fig. 2B.

The largest decrease in FGA was seen in the age group '30 to 34' (-45%, 2.24 to 1.24 DID), followed by the age groups '50 to 54' (-44%, 6.34 to 3.56) and '35 to 39 (-43%, 3.00 to 1.69). See Tables 2 and Fig. 2A. There were only two groups in which the FGA increased slightly, namely the '15 to 19' year olds (13%, 0.27 to 0.31), particularly driven by pipamperone (36%, 0.13 to 0.18) and melperon (40%, 0.02 to 0.03) and the '20 to 24' year olds (9%, 0.69 to 0.75), mainly due to increased prescribing of pipamperone (99%, 0.14 to 0.28) and prothipendyl (71%, 0.04 to 0.06).

In 2024, APM use by age groups peaked at 18.96 DID in the age group '60 to 64', followed by a decline in individuals aged 65 to 74. However, the rate increased again in the age group over 75 years, reaching a maximum of 26.55 DID in those at the age of 90 or older (Table 2; Fig. 3). SGA were prescribed more frequently than FGA

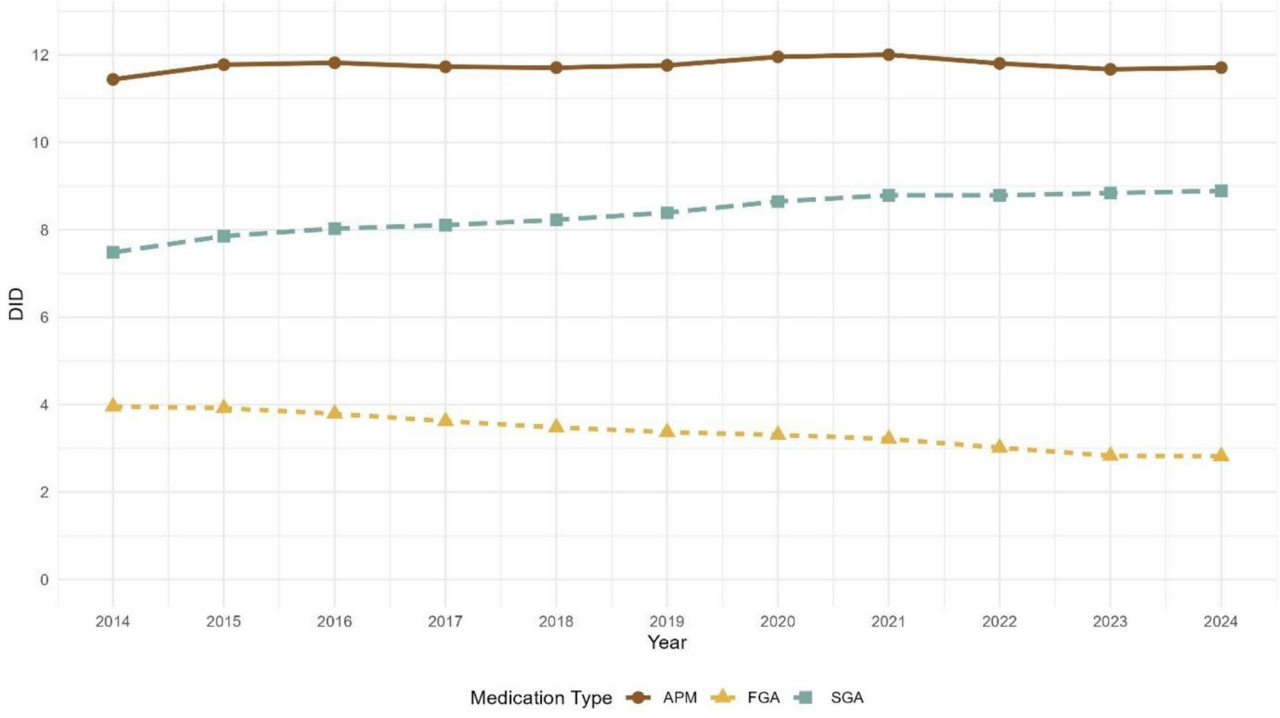


Fig. 1 Trends in antipsychotic medication use in Germany from 2014 to 2024, stratified by medication type. Abbreviations: APM, antipsychotic medication; DID, defined daily doses per 1,000 statutory health insurance-insured persons per day; FGA, first-generation antipsychotic; SGA: second-generation antipsychotic

Table 1 Trends in antipsychotic medication use in Germany from 2014 to 2024

	APM	FGA	SGA	Quetiapine	Olanzapine	Risperidone	Aripiprazole	Clozapine
DID 2014	11.44	3.96	7.48	2.07	1.58	1.41	0.62	0.63
DID 2024	11.71	2.82	8.89	2.47	1.98	1.38	1.28	0.56
Δ	2%	-29%	19%	19%	25%	-2%	106%	-11%
Estimate	0.015	-0.121	0.137	0.038	0.039	-0.004	0.063	-0.007
P-value	0.304	< 0.001	< 0.001	< 0.001	< 0.001	0.006	< 0.001	< 0.001
95% CI	(-0.016 to 0.047)	(-0131 to -0.111)	(0.112 to 0.162)	(0.031 to 0.045)	(0.033 to 0.045)	(-0.006 to -0.001)	(0.054 to 0.072)	(-0.008 to -0.005)

Abbreviations: APM, antipsychotic medication; CI, confidence interval; DID, defined daily doses per 1,000 statutory health insurance-insured persons per day; FGA, first-generation antipsychotic; Δ, percentage change in 2024 compared to 2014 values; SGA: second-generation antipsychotic

in all age groups except for the 90 + age group, where the use of FGA and SGA was almost equal (FGA 13.26 and SGA 13.29 DID) (Table 2).

Use of top 4 APM substances and clozapine

After filtering the top 4 APMs in 2024 and clozapine, a time trend analysis revealed that use of all these APMs increased, with the exception of risperidone and clozapine whose use decreased (Table 1).

Quetiapine´s use increased by 19% (2.07 to 2.47 DID, $p < 0.001$), and the age group in which the increase was most pronounced was the '65 to 69' (79%, 2.04 to 3.65) (Table 2).

The use of olanzapine increased by 25% (1.58 to 1.98 DID, $p < 0.001$), with young adults between 15 and 19 years showing the largest increase in use, at 71% (0.15 to 0.25 DID).

Aripiprazole was the APM which had the highest increase of all, at 106% (0.62 to 1.28 DID, $p < 0.001$). Among older adults aged 85 to 89, the increase was highest at 289% (0.15 to 0.58 DID), followed by an increase of 240% (0.14 to 0.48 DID) in the 90 + age group.

Risperidone´s use decreased slightly by 2% during the study period (1.41 to 1.38 DID, $p = 0.006$). The sharpest decline was observed in the age group '30 to 34', at 23% (1.17 to 0.90).

Clozapine´s use decreased by 11% (0.63 to 0.56 DID, $p < 0.001$). The sharpest decline was observed in the age group '30 to 34', by − 48% (0.90 to 0.47 DID), but in the age group '65 to 69' the use of clozapine increased by 47% (0.50 to 0.73 DID).

Use of APM by prescriber type

In 2024, the proportion of APM prescribed by general practitioners rose considerably with the patient´s age from 14% (2.01 DID, 40–44 years) being the lowest value of all age groups, to 60% (15.92 DID, 90 + years), the highest value. Accordingly, the proportion of APM prescribed by a psychiatrists/neurologists declined, from 64% (9.25 DID, 40–44 years) to 34% (8.97 DID, 90 + years). See Table 3; Fig. 4.

The five most frequently prescribed APMs in the 90 + age group in 2024 were risperidone, melperone, pipamperone, quetiapine, and olanzapine. For those APMs, the proportion of prescriptions issued by general practitioners increased with age. This increase was more pronounced for some substances, such as risperidone: from 16% (0.21 DID) of the prescriptions issued by general practitioners in the 40–44 age group to 60% (3.82 DID) in the 90 + age group, and less pronounced for others, such as olanzapine, from 16% (0.41 DID) of the prescriptions issued by general practitioners in the 40–44 age group, to 41% (0.50 DID) in the 90 + age group (Table 3).

Discussion

From 2014 to 2024 the use of SGA in Germany increased by 19%, while the use of FGA declined by 29%. The age groups in which antipsychotic use increased the most were younger adults (15 to 24 years) and older adults (60 to 74 years).

This trend towards an increased use of SGA might be, among others, due to several reasons:

1. A generally lower risk of extrapyramidal side effects of SGA compared to FGA.
2. Approval of new therapeutic indications and formulations in recent years (e.g. aripiprazole and quetiapine).
3. High volume of off-label use of SGA.

Generally, SGA are associated with fewer extrapyramidal side effects (e.g., tremors, akathisia) [4, 6, 12] however, they do have cardiometabolic side effects (e.g. weight gain, obesity, hypertension, glucose/lipid abnormalities). The observed increase in SGA use is particularly concerning in APM-naïve individuals starting antipsychotic medications at a young age, giving the potential to long-term cardiometabolic side effects [13–15].

Table 2 Trends in antipsychotic medication use in Germany by age group from 2014 to 2024

Age group	DID/ Δ	APM	FGA	SGA	Quetiapine	Olanzapine	Risperidone	Aripiprazole	Clozapine
0–14	DID 2014	0.51	0.14	0.37	0.04	0.02	0.22	0.04	0.00
	DID 2024	0.44	0.10	0.34	0.02	0.01	0.21	0.09	0.00
	Δ	**-14%**	**-32%**	**-7%**	**-55%**	**-50%**	**-3%**	**130%**	-
15–19	DID 2014	1.62	0.27	1.35	0.36	0.15	0.45	0.22	0.04
	DID 2024	2.13	0.31	1.82	0.46	0.25	0.44	0.55	0.03
	Δ	**32%**	**13%**	**35%**	**29%**	**71%**	**-1%**	**149%**	**-35%**
20–24	DID 2014	3.88	0.69	3.19	0.91	0.60	0.61	0.48	0.19
	DID 2024	4.99	0.75	4.24	1.13	0.91	0.65	0.96	0.15
	Δ	**29%**	**9%**	**33%**	**23%**	**51%**	**6%**	**100%**	**-22%**
25–29	DID 2014	6.81	1.36	5.44	1.51	1.04	0.86	0.75	0.47
	DID 2024	7.08	1.02	6.06	1.35	1.41	0.80	1.27	0.35
	Δ	**4%**	**-26%**	**11%**	**-11%**	**35%**	**-8%**	**69%**	**-26%**
30–34	DID 2014	10.60	2.24	8.36	2.15	1.67	1.17	1.09	0.90
	DID 2024	8.50	1.24	7.26	1.61	1.68	0.90	1.44	0.47
	Δ	**-20%**	**-45%**	**-13%**	**-25%**	**1%**	**-23%**	**32%**	**-48%**
35–39	DID 2014	12.51	3.00	9.52	2.47	1.94	1.33	1.13	1.05
	DID 2024	10.96	1.69	9.27	2.15	2.06	1.07	1.74	0.68
	Δ	**-12%**	**-43%**	**-3%**	**-13%**	**7%**	**-20%**	**54%**	**-36%**
40–44	DID 2014	13.96	3.92	10.04	2.77	2.08	1.43	1.06	1.07
	DID 2024	14.46	2.43	12.03	2.85	2.66	1.34	2.09	1.07
	Δ	**4%**	**-38%**	**20%**	**3%**	**27%**	**-6%**	**97%**	**0%**
45–49	DID 2014	15.88	5.12	10.77	2.98	2.34	1.57	0.96	1.18
	DID 2024	16.14	3.05	13.10	3.27	2.95	1.49	2.13	1.13
	Δ	**2%**	**-40%**	**22%**	**10%**	**26%**	**-5%**	**122%**	**-5%**
50–54	DID 2014	17.78	6.34	11.43	3.16	2.57	1.76	0.91	1.20
	DID 2024	17.14	3.56	13.57	3.72	3.09	1.59	2.01	1.05
	Δ	**-4%**	**-44%**	**19%**	**18%**	**20%**	**-10%**	**122%**	**-13%**
55–59	DID 2014	17.88	7.02	10.86	3.04	2.53	1.76	0.75	1.04
	DID 2024	18.28	4.19	14.09	4.07	3.31	1.72	1.89	1.08
	Δ	**2%**	**-40%**	**30%**	**34%**	**31%**	**-2%**	**151%**	**4%**
60–64	DID 2014	15.83	6.40	9.43	2.66	2.31	1.62	0.57	0.75
	DID 2024	18.96	4.86	14.10	4.19	3.38	1.86	1.71	0.98
	Δ	**20%**	**-24%**	**49%**	**57%**	**47%**	**15%**	**200%**	**32%**

Table 2 (continued)

Age group	DID/ Δ	APM	FGA	SGA	Quetiapine	Olanzapine	Risperidone	Aripiprazole	Clozapine
65–69	DID 2014	12.49	5.17	7.32	2.04	1.84	1.35	0.41	0.50
	DID 2024	16.72	4.54	12.17	3.65	3.07	1.75	1.38	0.73
	Δ	**34%**	**-12%**	**66%**	**79%**	**67%**	**30%**	**235%**	**47%**
70–74	DID 2014	11.43	4.57	6.86	2.05	1.68	1.40	0.32	0.35
	DID 2024	13.92	3.96	9.96	3.13	2.47	1.68	1.07	0.45
	Δ	**22%**	**-13%**	**45%**	**53%**	**47%**	**20%**	**239%**	**29%**
75–79	DID 2014	11.84	4.75	7.08	2.14	1.50	1.80	0.27	0.25
	DID 2024	12.63	4.00	8.64	2.92	1.93	1.88	0.78	0.25
	Δ	**7%**	**-16%**	**22%**	**36%**	**29%**	**5%**	**191%**	**-3%**
80–84	DID 2014	14.49	6.32	8.17	2.42	1.36	2.80	0.21	0.16
	DID 2024	14.30	5.30	9.01	3.28	1.62	2.66	0.64	0.14
	Δ	**-1%**	**-16%**	**10%**	**36%**	**20%**	**-5%**	**202%**	**-11%**
85–89	DID 2014	19.46	9.14	10.32	2.78	1.33	4.61	0.15	0.10
	DID 2024	18.74	8.02	10.71	3.87	1.47	4.10	0.58	0.08
	Δ	**-4%**	**-12%**	**4%**	**39%**	**11%**	**-11%**	**289%**	**-15%**
90+	DID 2014	26.91	13.79	13.12	3.26	1.29	7.01	0.14	0.09
	DID 2024	26.55	13.26	13.29	4.60	1.23	6.38	0.48	0.04
	Δ	**-1%**	**-4%**	**1%**	**41%**	**-5%**	**-9%**	**240%**	**-60%**

Abbreviations: APM, antipsychotic medication; DID, defined daily doses per 1,000 statutory health insurance-insured persons per day; FGA, first-generation antipsychotic; Δ, percentage change in 2024 compared to 2014 values; SGA: second-generation antipsychotic

The use of SGAs continued to increase during the study period. The S3 guideline for schizophrenia by the German Society for Psychiatry and Psychotherapy, Psychosomatics and Neurology [32] published in 2019 recommend the individualized selection of antipsychotic medications based on tolerability and clinical characteristics rather than favouring SGAs over FGAs.

Aripiprazole's use increased significantly (by 106%) during the study period. This might be because in 2013 the once-monthly, long-acting injectable formulation was approved as maintenance treatment for schizophrenia in adults stabilized with oral aripiprazole [16–18]. In the same year, the indication of oral aripiprazole was extended for the treatment up to 12 weeks of moderate to severe manic episodes in bipolar disorder in adolescents aged 13 and older [19, 20]. The availability of generic oral formulations of aripiprazole in 2015 might have also contributed to this increase [21]. Especially, this increase occurred despite the 2016 FDA warning on the risk of impulse control disorders (e.g., pathological gambling) associated with aripiprazole, and the inclusion of this warning in the summary of product characteristics (SmPC) by the European Medicines Agency (EMA) in 2017 [22–25].

Another possible explanation for the significant increase in the use of aripiprazole is its generally favourable safety and tolerability profile compared to other SGA. Aripiprazole is associated with a lower risk of weight gain, metabolic disorders, and cardiovascular effects, carries a minimal risk of extrapyramidal symptoms, and is not associated with hyperprolactinemia [26]. These characteristics may make it a preferred choice, particularly for older adults with comorbid physical conditions or for patients for whom minimizing anticholinergic burden, risk of falls, or cognitive effects is important. Such a "more favourable" side effect profile may therefore have contributed to its increasing use over time. Quetiapine´s increase might be due to its 2009 approval by the Federal Institute for Drugs and Medical Devices for the prevention of relapses in bipolar disorder [27] and as augmentation therapy for major depressive disorder (MDD) in the event of an inadequate response to standard antidepressants [28].

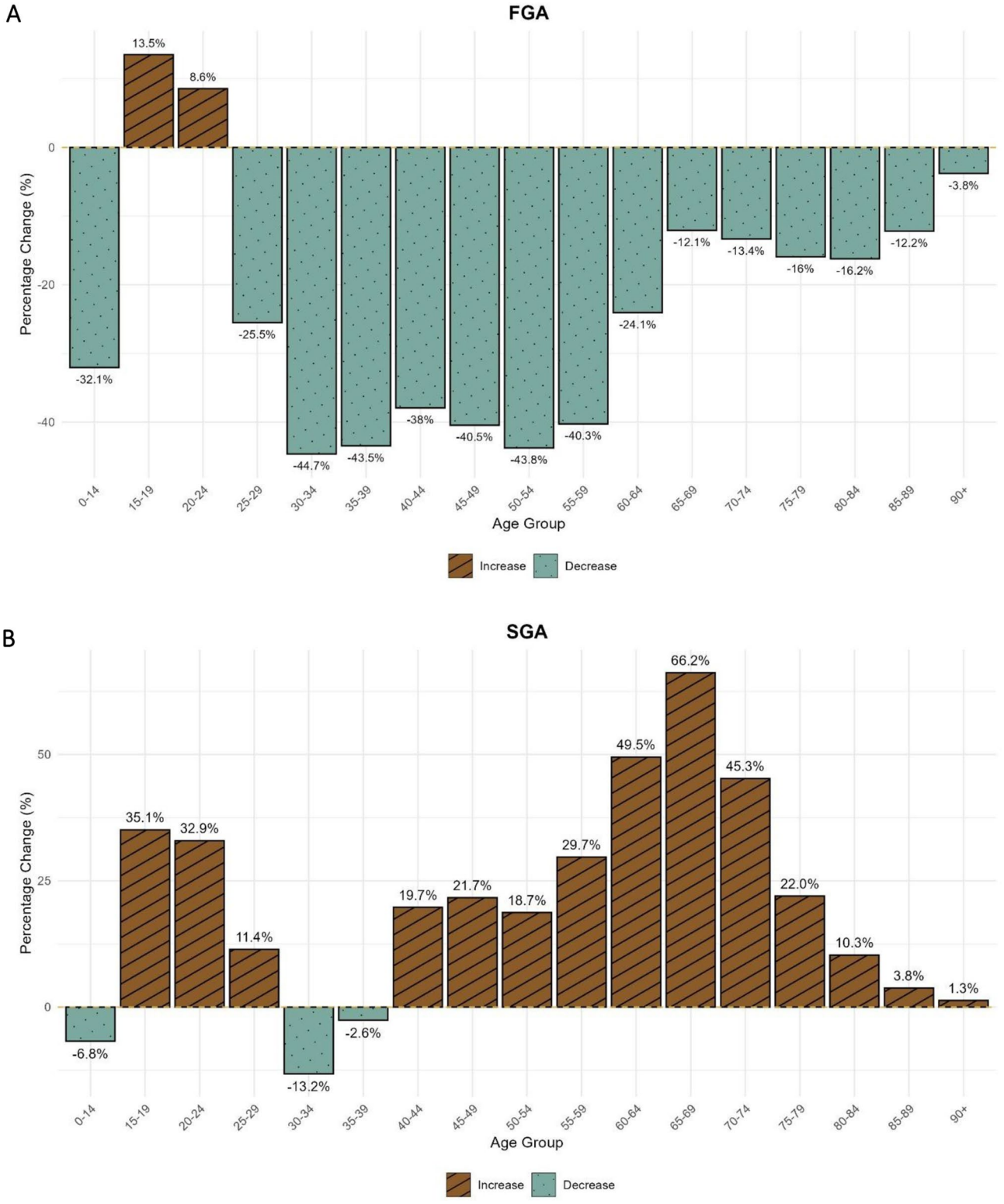


Fig. 2 Change in the use of first- and second-generation antipsychotics by age group in 2024 compared to 2014. **A**: Percentage change (in DID) of FGA; **B**: Percentage change (in DID) of SGA. Abbreviations: DID, defined daily doses per 1,000 statutory health insurance-insured persons per day; FGA, first-generation antipsychotic; SGA: second-generation antipsychotic

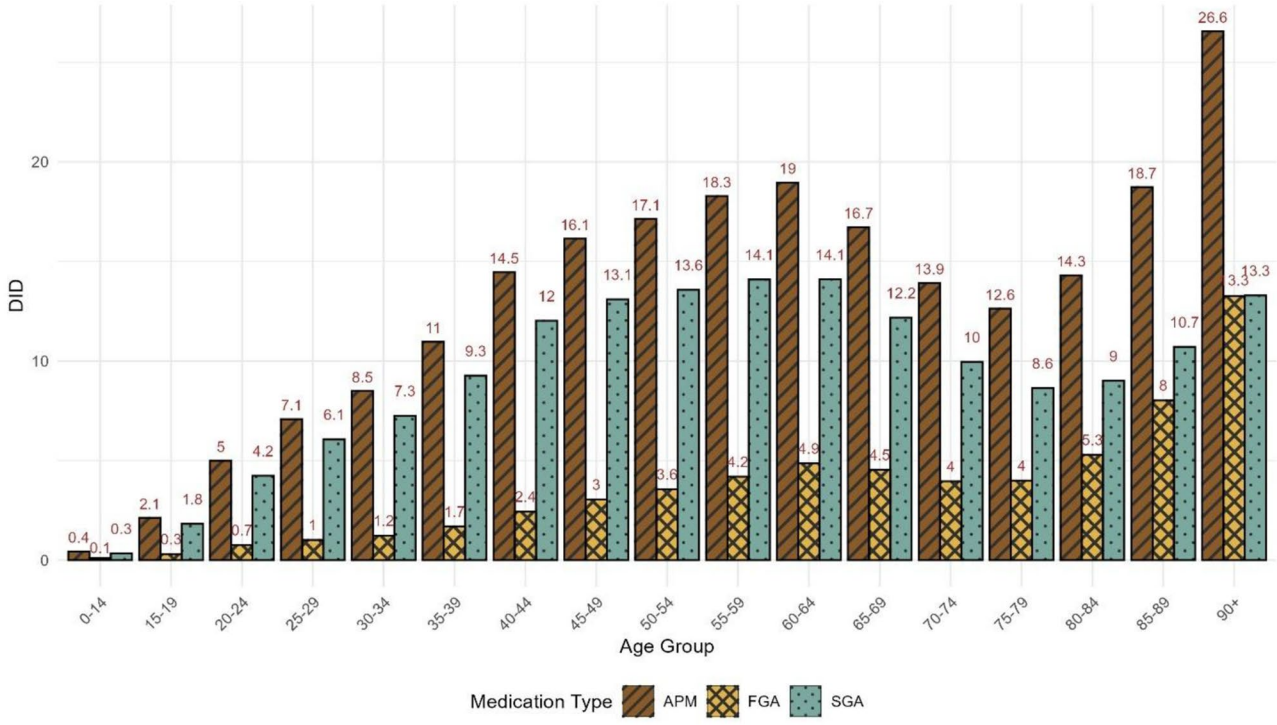


Fig. 3 Antipsychotic medication use per age group and medication type in Germany in 2024. Abbreviations: APM, antipsychotic medication; DID, defined daily doses per 1,000 statutory health insurance-insured persons per day; FGA, first-generation antipsychotic; SGA: second-generation antipsychotic

The use of olanzapine has increased over the past 11 years. While this increase cannot be explained by new regulatory approvals or formal indications, it may be the result of olanzapine commonly prescribed off-label for patients with affective disorders [29] and eating disorders [30]. In particular, the increase in olanzapine DIDs among young adults is noteworthy. Olanzapine is not approved by the EMA for children and adolescents under 18 years of age [31], but the German S3 guideline on schizophrenia refers to evidence of efficacy and, after careful risk–benefit evaluation, allows off-label use when clinically indicated [32]. Additionally, German guidelines on eating disorders suggest that olanzapine can reduce obsessive thoughts and compulsive behaviour in anorexia nervosa [33], which may further explain its increased use in this population. Similar prescribing patterns have been reported in the United Kingdom, where psychotropic drugs were frequently prescribed to children and adolescents with eating disorders in inpatient psychiatric facilities, both as regular medication and prn (as required) use [34].

The observed decline in risperidone use is remarkable, particularly in the 30–34-year age group, where the largest decrease was observed. A plausible explanation is the risk of hyperprolactinaemia, a common side effect of risperidone, which may be of particular concern in females of child-bearing potential [35]. Although patient-level data are not available to assess sex-specific patterns, it is plausible that prescribers are increasingly cautious in this group. Future studies with sex-stratified data could clarify whether the decline disproportionately affects female patients. In a nationwide German study involving 17,641 children and adolescents aged 0 to 17, those taking psychotropic drugs had higher mean scores in the screenings for emotional or behavioural problems than the total sample. However, 40% of these children showed no abnormal scores. The study also found a high rate of off-label use of antipsychotics, showing an increase in the use of the SGA and none of them, except risperidone, were approved for use in young people at the time of the study. The indications of APM were mainly tic disorder and behavioural problems particularly, aggression or hyperactivity/attention deficit symptoms, therefore primarily used to treat behavioural symptoms rather than psychotic disorders [36]. Another study also found that the annual proportion of off-label APM prescriptions in the paediatric population ranged from 61.0% to 69.5%, with APMs being prescribed primarily to treat aggressive and impulsive behaviours in patients with hyperkinetic disorders [37].

Similar results were observed in the United Kingdom and Belgium, where a high proportion of people were prescribed antipsychotics without any diagnoses of psychotic or bipolar disorders [38, 39].

Table 3 Antipsychotic medication use by prescriber type in Germany in 2024: comparison between age groups 40–44 and 90+

Medication	Age group						Age group					
	40–44						90+					
	Neurologist		General practitioner		Other		Neurologist		General practitioner		Other	
	Psychiatrist						Psychiatrist					
	DID	DID (%)	DID	DID (%)	DID	DID (%)	DID	DID (%)	DID	DID (%)	DID	DID (%)
APM	9.25	64%	2.01	14%	3.18	22%	8.97	34%	15.92	60%	1.66	6%
FGA	1.48	61%	0.39	16%	0.56	23%	3.73	28%	8.72	66%	0.81	6%
SGA	7.77	65%	1.63	13%	2.62	22%	5.24	40%	7.20	54%	0.85	6%
Quetiapine	1.78	62%	0.58	21%	0.49	17%	1.94	42%	2.34	51%	0.32	7%
Olanzapine	1.66	62%	0.41	16%	0.59	22%	0.59	49%	0.50	41%	0.13	10%
Risperidone	0.86	64%	0.21	16%	0.27	20%	2.23	35%	3.82	60%	0.33	5%
Pipamperone	0.28	58%	0.12	24%	0.09	18%	1.9	31%	3.87	64%	0.33	5%
Melperone	0.07	57%	0.04	30%	0.02	13%	1.21	23%	3.75	73%	0.21	4%

Abbreviations: APM, antipsychotic medication; DID, defined daily doses per 1,000 statutory health insurance-insured persons per day; FGA, first-generation antipsychotic; SGA: second-generation antipsychotic

The age-specific patterns of antipsychotic use also deserve attention. In Germany, the rate of APM use gradually increased with age until the age of 60 to 64 years, then slightly declined before increasing again more sharply from the age of 75 years old reaching a maximum at the age of 90 or older. This age-dependent pattern echoes the findings of a US study that found a similar relapse in antipsychotic use between the ages of 55 and 65 [40]. This study suggested the possibility that shifts in the prevalence or course of major mood disorders might have contributed to the decline. The study authors cited evidence that older adults with bipolar disorder tend to have fewer manic symptoms [41] exhibit less frequently psychotic features and are less often treated with antipsychotic medications [42]. Yet, some studies, have found minimal differences in the acute symptoms of bipolar disorder in older versus younger adults [43].

Antipsychotic medication usage in the very old group might be related to increased dementia rates. According to the 2023 estimates from the German Center for Neurodegenerative Diseases (DZNE), the dementia prevalence rates start rising from the mid-seventies from 5% of women and 6% of men, to 29% and 22%, respectively, among those aged 90 or older [44].

Antipsychotic medications are commonly used to treat behavioural and psychological symptoms of dementia (BPSD). These symptoms include agitation, aggression, psychosis and inappropriate behaviours. Haloperidol and risperidone are the only antipsychotics approved for the treatment of BPSD in some countries [45]. In Germany, risperidone is approved for the treatment of aggressive behaviour in Alzheimer's disease when non-pharmacological measures are inadequate and there is a risk of harm to the patient or others. However, it is not approved for psychosis associated with dementia. Haloperidol is licensed for the treatment of psychotic symptoms in Alzheimer's disease that do not respond adequately to non-pharmacological treatments and pose a risk to the patient or others. According to German guidelines, antipsychotics prescribed for the treatment of BPSD should be used at the lowest effective dose and for a limited duration [46].

Despite long-standing safety concerns, including a 2004 European Medicines Agency (EMA) warning on stroke and mortality risk with olanzapine and risperidone and a 2009 expanded warning covering all APMs in dementia [47, 48] the prescribing behaviour in Germany appears to be largely unchanged [49].

Macdonald et al. [50] found an increase in antipsychotic use in care homes during the COVID-19 pandemic, that matched a peak in use of other end-of-life medicines. However, as none of the common antipsychotics prescribed in our + 90 population, are used for

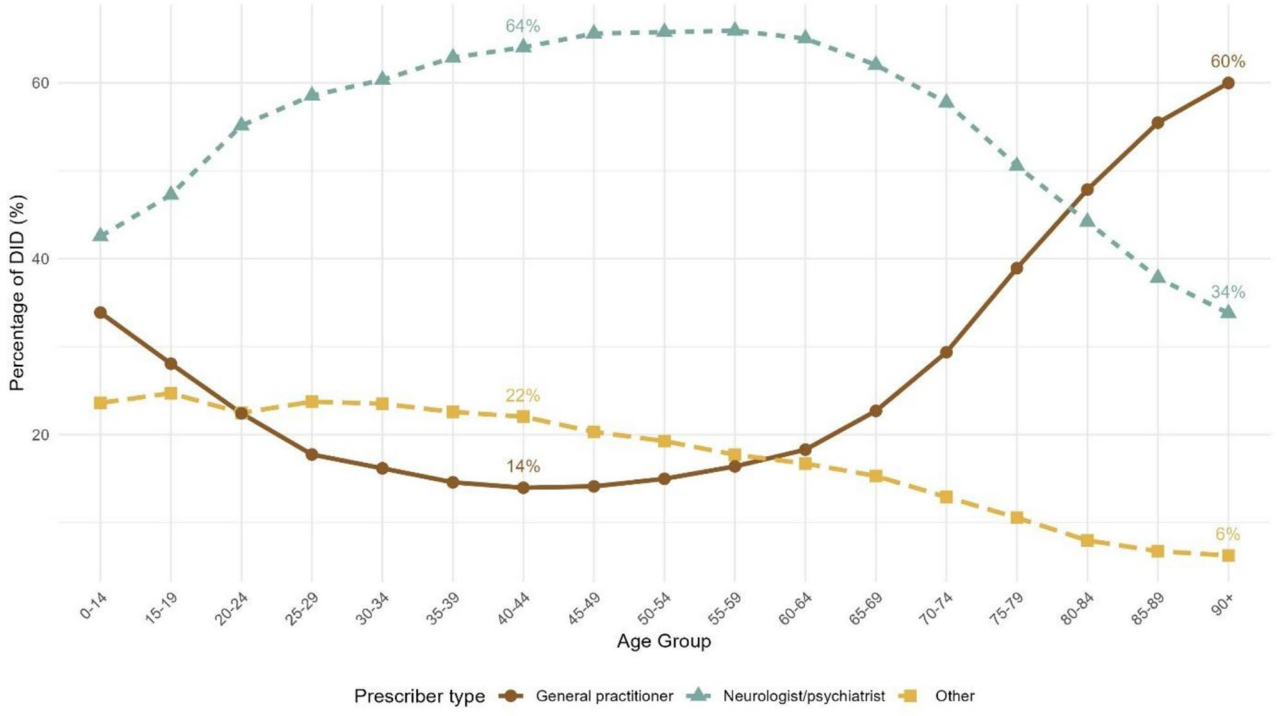


Fig. 4 Percentage of APM (DID) by prescriber type across different age groups in Germany in 2024. Abbreviations: APM, antipsychotic medication; DID, defined daily doses per 1,000 statutory health insurance-insured persons per day

palliative care, the increased use is more likely due to prescribing for dementia.

Recent studies suggest that the COVID-19 pandemic may have had an impact on the prescription of psychotropic drugs. For example, Francesca Gallinella et al. [51] reported an increase in prescriptions of psychotropic drugs for children and adolescents in 2020 compared to the previous year. In addition, other studies have pointed to changes in the prescription of antipsychotics during the pandemic [52], particularly among vulnerable populations such as people with dementia.

Clozapine is highly effective for treatment-resistant schizophrenia (TRS) but is generally underutilized [53, 54], mainly due to the risk of severe neutropenia and agranulocytosis, which needs strict blood count monitoring and may be a significant barrier to its use.

It is important to know that clozapine has long been recognized as a treatment for TRS but although in 2019 the German S3 schizophrenia guideline [55] explicitly recommended clozapine as the first-line treatment for patients with TRS clozapine use still remained underutilized and its use has even decreased in some age groups.

Clozapine-induced neutropenia can occur at any time during treatment but occurs most frequently during the first year of treatment, with the highest risk in the first 18 weeks [56]. In 2025, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has recommended less frequent blood count monitoring for patients without neutropenia, every 12 weeks after one year of treatment and annually after two years. Monitoring is now based only on the absolute neutrophil count, which is a more specific and clinically relevant marker, and the routine white blood cell count monitoring is no longer required. Our study includes data only up to 2024, therefore we were unable to assess the impact of these recent regulation changes but, evaluating their influence on clozapine prescribing patterns would be an important focus for future analyses.

Strengths and limitations

The main limitation of this study is the lack of data at the individual patient level. Thus, since we have no information about the diagnosis, we cannot assess whether or not the antipsychotics were used on-label or off-label.

As the DID is based on the daily doses for adults, the interpretation of antipsychotic consumption in the age group 0–15 years is difficult, as the lower paediatric dosing might lead to an underestimation of the actual consumption in this population.

A similar limitation may apply to the older adult population. Antipsychotics prescribed to older adults, particularly for BPSD, are often administered in doses below the DDD [57, 58]. Consequently, this may also lead to an underestimation of the actual prevalence of antipsychotic use in older patients. Antipsychotics are frequently used in children and adolescents for

indications other than primary psychosis, including behavioural symptoms associated with autism spectrum disorders and as adjunctive therapy for treatment-resistant obsessive-compulsive disorder [59], with evidence supporting the efficacy of agents such as aripiprazole and risperidone in these contexts. This highlights why caution is needed when interpreting DDD-based use in these age groups, as the doses prescribed for these indications may be lower and outside the approved indications.

Furthermore, prescription data reflect medications dispensed, not those actually taken, so we cannot determine whether patients adhered to prescribed treatment. This is an important limitation, especially given the high rates of medication non-adherence in mental health care [60].

One limitation of our study is that the age distribution and the health status, of the remaining 13% of the population which is not covered by the SHI is unknown and may differ from that of the 87% covered in the dataset.

On the other hand, the greatest strengths of this study are the availability of very recent (2024) data and large coverage, as the data covers more than 80% (until June 2019) and more than 95% of German community pharmacies (from July 2019), representing 87% of the total population.

Conclusions

The use of SGAs continued to increase during the study period.

The sharp increase in younger adults and the persistently high use among older people raises concerns about the long-term safety and diagnostic justification, particularly in the off-label contexts. The observed decline in clozapine use in most age groups raises concerns about underutilization of an evidence-based treatment and underscores the need to address prescribing barriers. These trends indicate a need for:

- More robust evidence for off-label use
- Clearer guidance on prescribing in young and older adults
- Continuous education and monitoring of prescribing behaviour
- Future analyses to assess the impact of clozapine recent regulatory changes

Abbreviations

APM	Antipsychotic medication
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
BPSD	Behavioural and psychological symptoms of dementia
DAPI	German Institute for Drug Use Evaluation
DDD	Defined daily doses
DID	Defined daily doses per 1,000 statutory health insured persons per day
DZNE	German Center for Neurodegenerative Diseases
EMA	European Medicines Agency
FGA	First-generation antipsychotic
PRAC	Pharmacovigilance Risk Assessment Committee
SGA	Second-generation antipsychotic
SH	Statutory health
TRS	Treatment resistant schizophrenia

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Author contributions

Author AED designed the study and conducted the literature search. AED retrieved the data together with MK. AED performed the statistical analyses, which were reviewed by MK. AED drafted the initial version of the manuscript, and MK and MS provided critical revisions. All authors contributed to and approved the final version of the manuscript.

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Data availability

The datasets generated and/or analysed during the current study are not publicly available but may be made available upon reasonable request and with permission from the DAPI.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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