2001–2021 Comparative Persistence of Oral Antipsychotics in Patients Initiating Treatment: Superiority of Clozapine in Time-to-Treatment Discontinuation

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ABSTRACT

Background Continuous antipsychotic (AP) therapy is crucial for managing psychotic disorders, and its early interruption reflects the drug's failure. Real-world epidemiological research is essential for confirming experimental data and generating new research hypotheses.

Methods The persistence of oral APs in a large population sample from 2000 to 2021 was analyzed by comparing AP prescriptions over this period across four Italian provinces, using dispensing data linked via a record-linkage procedure among regional healthcare utilization databases. We calculated personalized daily dosages and assessed time-to-treatment discontinuation over a 3-month period for patients initiating AP treatment. Treatment persistence was evaluated using Kaplan-Meier curves and Cox regression, with adjustments for age and sex.

Results Second-generation antipsychotics (SGAs) were favored over first-generation antipsychotics (FGAs), with olanzapine as the most prescribed. Within the study time frame, 42,434 individuals were prescribed a new continuous AP regimen. The analysis revealed 24 significant differences within 28 comparisons. As a class, SGAs demonstrated better treatment persistence than FGAs (HR: 0.76; 95 %CI: 0.73, 0.79). Clozapine stood out for its superior persistence, surpassing all other SGAs, notably olanzapine (HR: 0.85; 95 %CI: 0.79–0.91) and risperidone (HR: 0.80; 95 %CI: 0.74–0.87). Olanzapine and aripiprazole showed better results than both risperidone and quetiapine. Quetiapine showed inferior 3-month persistence in all pairwise comparisons.

Conclusion The study results provide insight into the performance dynamics among SGAs: clozapine, despite being one of the less frequently dispensed APs in our sample, emerged as a significant prescription choice. The significance of pharmacoepidemiological studies in complementing experimental findings is also underscored.

Introduction

Antipsychotic (AP) long-term prescription is one of the cornerstones of treatment for psychotic disorders. Patients on AP medications do better overall; early cessation often results in higher relapse rates, hospitalization, and risk of death and violence [1–3]. Originally for psychosis, the use of APs has expanded to address psychotic symptoms in various mental disorders, behavioral disturbances in dementia, pervasive developmental disorders, and as adjuncts to antidepressants or mood stabilizers in major affective disorders [4].

First-generation antipsychotics (FGAs) are effective against psychotic symptoms but often cause significant neuroleptic side effects [5, 6]. Second-generation APs (SGAs) were introduced as more efficacious and better tolerated but can lead to serious metabolic side effects like weight gain and diabetes [7]. A meta-analyses by Leucht et al. highlighted efficacy differences among APs, with the SGAs clozapine, amisulpride, olanzapine, and risperidone showing superior performance, despite their distinct side-effect profiles [8, 9]. Similarly, Huhn et al. found clozapine, amisulpride, zotepine, olanzapine, and risperidone to be superior to the other APs in terms of efficacy measures [10]. In terms of effectiveness, the meta-analyses by Kishimoto et al. showed that SGAs, particularly clozapine, olanzapine, and risperidone, were superior in reducing all-cause discontinuation compared to FGAs and other SGAs in direct comparisons [11, 12].

Treatment discontinuation is a broad measure of effectiveness, safety, and tolerability, often linked to efficacy issues, adverse events, or patient unwillingness to continue treatment. This pragmatic endpoint is used as the primary outcome in many non-industry-funded RCTs evaluating APs in schizophrenia [13–22]. Independent real-world trials have shown that older APs outperform expectations set by earlier efficacy trials and meta-analyses, suggesting that while newer APs are an advancement, they do not mark a revolutionary breakthrough in effectiveness [23]. Industry-sponsored RCTs and related meta-analyses, often influenced by financial conflicts of interest, face scrutiny over potential biases and methodological issues, casting doubt on their reliability and impartiality [24–26]. These caveats highlight the utility of the integration of both experimental and observational evidence to inform treatment decision-making [27, 28]. Pharmaco-epidemiological data offers a potent lens to substantiate meta-analytic findings on drug efficacy through real-world effectiveness data. Our previous investigation into reboxetine, extensively prescribed in Europe for depression, underscores this point. Eyding et al. (2010) determined it to be ineffective and potentially harmful, findings that our pharmaco-epidemiological research supported, highlighting low treatment retention [29, 30]. This case illustrates how pharmaco-epidemiological data can not only reinforce but also anticipate issues with drug responses before a comprehensive experimental dataset is available.

Our study aims to compare oral AP dispensing trends in a large population sample from 2000 to 2021, with a primary focus on evidencing the superiority of SGAs over FGAs, in line with prior experimental research [8–12]. To better contextualize AP persistence within broader epidemiological shifts, we initially examined 2000-2021 general epidemiological trends in AP use. We then targeted our primary objective by directly comparing time-to-treatment discontinuation (TTD) of FGAs and SGAs and conducted detailed comparisons between individual drugs.

Materials and Methods

Administrative healthcare database variables

This study utilized the computerized Healthcare Utilization database of Lombardy (Lombardy DB), part of an automated system implemented across Italian regions for healthcare service management. The Lombardy DB systematically collects information on residents who are beneficiaries of the National Health Service (SSN), encompassing socio-demographic details (such as gender, age, education level, etc.), outpatient drug prescriptions, hospital discharge diagnoses from both public and private facilities, specialist visits, and diagnostic tests covered fully or partially by the SSN. The Lombardy system of automated Healthcare Utilization databases comprises: 1. an archive of all residents receiving SSN assistance, virtually the entire resident population, with demographic and administrative data; 2. an archive including all certifications of chronic diseases for exemption from co-payment; 3. an archive of all hospital discharge forms from public or private hospitals, detailing all diagnoses related to hospitalization; 4. an archive of all outpatient drug prescriptions reimbursable by the SSN. Through a record-linkage procedure facilitated by a unique individual identification code, which is used across all databases for each SSN beneficiary and automatically anonymized for privacy, it is possible to interconnect these regional HCU databases. This linkage enables the tracking of complete healthcare journey of each patient. Data were registered and stored in compliance with both Italian and European General Data Protection Regulations. The Lombardy DB contains information about the number of dispensed Defined Daily Doses (DDD) of all outpatient prescription-based medications. DDDs are assigned and reviewed by researchers of the World Health Organization Collaborating Centre of Drug Statistics Methodology [31]. Importantly, registered dispensations correspond to a variable number of drug's boxes/packages, ranging from one to two, based on the specific AP and prescribing practices. Additionally, for each dispensation, both the number of boxes/packages and the number of DDDs generated are recorded, providing a comprehensive view of the medication dispensed [31].

Lombardy DB is routinely updated for administrative reasons. Briefly, for a drug to be reimbursed by the Italian National Health Service (Servizio Sanitario Nazionale, SSN), the patients need a prescription from their general practitioner (GP) or a SSN specialist and then get the medicines free of charge from retail pharmacies. Private psychiatrists or neurologists usually send their recommendations for drug treatment to GPs, who then complete the prescription forms. Each local pharmacy provides these prescriptions to the Regional Health Authority to get reimbursed; incomplete or incorrect reporting leads to legal consequences. The Regional Health Authority electronically stores these prescriptions in the Lombardy DB. Information on age and gender is available, but diagnoses related to prescriptions are not, as only those linked to hospital discharge records, as previously mentioned, are accessible. The database collects only community prescriptions and no information on drugs prescribed during admission to hospital or stay in nursing homes is available.

AP use prevalence and incidence were calculated as percentages of the resident population, considering those with three or more

AP dispensations yearly for prevalence and the subgroup of those who did not have any prescription for the same AP in the preceding year for incidence. All measures of oral APs dispensing were assessed based on the Anatomical Therapeutic Chemical classification (ATC) code [31] (ATC code: N05, Lithium excluded). Data on patients' sex, age, place of residence, date of purchase, drug information were extracted. For the primary analysis, the following two groups were compared: 1) SGAs (amisulpride-N05AL05, clozapine-N05AH02, olanzapine-N05AH03, risperidone/paliperidone-N05AX08/13, aripiprazole-N05AX12); 2) FGAs (haloperidol-N05AD01, other FGAs: N05AA/N05AB/N05AC/N05AD/N05AF/N05AG/N05AL).

Study setting and population

Prescriptions of APs dispensed to the adult population of four provinces in the Lombardy region, Northern Italy, were analyzed on the basis of a population-based database of dispensing records from January 1, 2000 to December 31, 2021. The study provinces directly align with the catchment areas of four Local Health Units (LHUs): the Metropolitan City of Milan, Sondrio, Brescia, and Pavia. Lombardy is the largest Italian region, with a population of about 10 million inhabitants. Adults living in the study areas remained stable in number across the years and totaled around 5 million in both 2000 and 2021, accounting for 50 % of the adult population of the region at the end of the study period.

By virtue of the universal coverage provided by the SSN, all residents aged 18–65 years were eligible for inclusion in the study, thereby encompassing the entire resident population within this age range. For each AP analyzed annually, the study included: (a) all individuals initiating AP treatment, defined as those who had not received any AP prescriptions in the year preceding the start of the observation period and (b) all individuals who were dispensed the specified AP at least three times, were identified as continuous users.

Personalized daily dosage (PDD) and time-to-treatment discontinuation Analysis

For the analysis, we identified continuous AP treatment periods by linking the DDDs from the first two dispensations of each prescription event in the dataset. This method aggregates the DDDs of each dispensed medication package within these initial dispensations to form a continuous timeline of AP use. If the second dispensing occurred at or before the end of the initial dispensation's DDDs, the two dispensations were directly linked (▶ **Fig. 1**, Case A). However, in cases where gaps between dispensations were observed, we addressed these by utilizing two previously validated corrections: the 'one-sixth rule' and a 30-day time margin (▶ **Fig. 1**, Cases B and C, respectively) [32, 33]. Under these conditions, dispensations were linked into continuous treatment periods if either the DDDs from the first dispensation, plus a period equal to one-sixth of the total DDDs dispensed, overlapped with the date of the second dispensation (▶ **Fig. 1**, Case B), or if the second dispensation occurred within a 30-day interval following the first (▶ **Fig. 1**, Case C). Prescription events that did not meet the study criteria due to excessive DDD gaps between the first two dispensations were excluded from the analysis, as it was not feasible to calculate PDDs for these instances.

To calculate the PDD, we aggregated all DDDs received within the initial treatment periods determined by linking the first two AP dispensations for each patient [34]. This total was then divided by the duration of these linked treatment periods (refer to ▶ **Fig. 1**, Cases A, B, and C.). The PDDs were then applied to assess time to

▶ **Fig. 1** The one-sixth and the one-month's gap rules for linkage of APs' dispensations into treatments' periods.

treatment discontinuation (TTD) for each participant, utilizing the same 'one-sixth rule' and a 30-day margin to manage gaps between dispensations and ensure a continuous treatment timeline. To prevent overestimation of treatment durations and dose accumulation, PDDs from preceding dispensations were adjusted and reset at the date of each new dispensing event.

For each drug, our analysis included only the first continuous prescribing event for each individual. Thus, a subject could appear multiple times in the analysis only if they had other prescribing events with different drugs. Additionally, only the first prescribing event for the same individual within the same class (SGA or FGA) was included.

For additional details on the study's population selection, treatment duration, and discontinuation algorithm, see **Supplementary Document S1**.

The primary analysis of TTD for the selected oral APs was conducted over a 3-month period. This duration has been chosen to enable the identification of significant differences in treatment outcomes, should they exist. This relatively brief follow-up period reduces the likelihood of inaccurately classifying cases as treatment failures—which could occur if patients discontinue their medication upon completing their prescribed treatment or due to sufficient symptom improvement. Such an approach promotes a more precise and meaningful evaluation of treatment persistence and discontinuation rates. We also conducted secondary analyses on TTD over the entire 20-year study, particularly assessing at 2, 5, and 20 years to determine if initial differences persisted over time.

Discontinuation of the drug and cessation of AP therapy, as well as switching to another AP or a long-acting formulation of the same drug, were considered discontinuations of oral treatment. This reflected a deliberate prescribing decision, likely due to insufficient clinical response or clinically significant side effects, poor medication adherence, or the need for more stable drug plasma levels.

To assess the primary objective, Kaplan-Meier survival analysis was employed to compare the duration of AP treatment among different APs. This approach estimated the distribution of treatment duration, adjusting survival functions for age and sex. Cases when individuals passed away, relocated to another region or reached the end of the study period were treated as censored instances. We utilized the Log-Rank test for comparing survival curves among different AP treatments at the 3-month benchmark, aiming to identify any significant disparities in treatment duration. The Cox regression model was used to calculate both unadjusted and adjusted hazard ratios (HRs and HRad, respectively), with 95 % confidence intervals (CIs). This adjustment accounted for age and sex as primary variables, and in separate models, it further adjusted for the degree of AP polypharmacy at 3 months and for the Study Period (Year of Study Entry). Using separate models helps assess the impact of each variable set independently, to the advantage of easier interpretation of the results. The level of AP polypharmacy was defined based on the occurrence of at least three concurrent dispensations of distinct APs (ATC code: N05, Lithium excluded) during any analyzed treatment period or the overlap of more than one AP prescribing event. To account for the multiple comparisons and control the false discovery rate, we applied the Benjamini-Hochberg method. This approach sequentially adjusts p-values, thereby reducing the likelihood of type I errors by considering the rank and quantity of comparisons made.

All statistical tests were performed using SAS software, SAS Institute Inc., Cary, NC, USA.

Data ownership, study funding, and reporting

This study was performed on behalf of the EPIFARM-Elderly project on drug prescription in Lombardy which is a large pharmacoepidemiological collaborative project on drug prescription in the elderly living in the Lombardy Region [35]. The present study had not yet received any specific grant or support from any funding agency. Study data belong to the Regional Health Ministry and are stored and managed by the Istituto di Ricerche Farmacologiche 'Mario Negri' IRCCS. An exemption from obtaining patients' informed consent due to organizational constraints is allowed by Italian privacy regulations for scientific research.

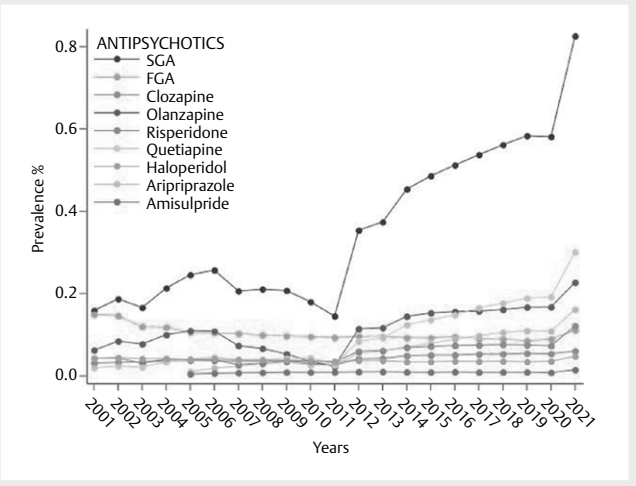
The study's planning, conducting, and reporting align with the National Institute for Health and Care Excellence (NICE) Real-World Evidence (RWE) framework, and incorporating a detailed protocol developed prior to analysis [36]. We also adhered to the RECORD-PE guidelines for reporting our results, with the RECORD-PE checklist provided in **Supplementary Document S1** for transparency [37].

Results

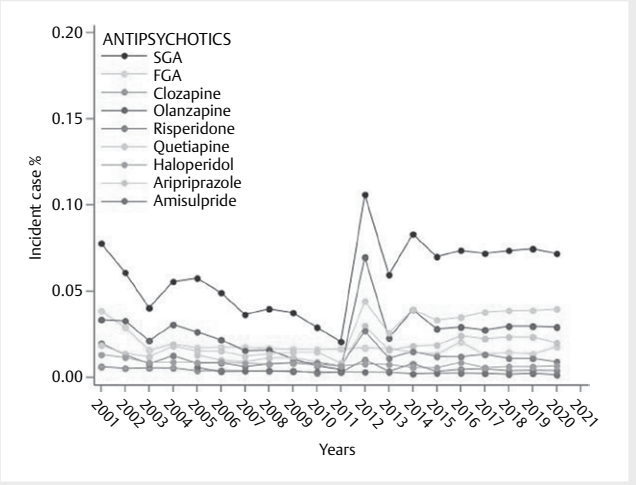
▶ **Fig. 2** and ▶ **Fig. 3**, respectively, depict the annual AP use prevalence and incidence from 2001 to 2021. The prevalent graph demonstrates a pronounced increase in SGA dispensations, dominating by 2021, while FGAs maintain a relatively consistent but lesser prevalence throughout the period. Among individual drugs, risperidone and aripiprazole both exhibit a gradual increase in their dispensation rates. Olanzapine, notably, sees a decline in prescriptions between 2006 and 2011, followed by a resurgence. After 2011, quetiapine also saw a significant increase in its use, becoming the most dispensed AP drug by 2021. Clozapine and amisulpride have remained relatively stable over the years, but with prescription rates lower and comparable to those of FGAs. The incidence graph illustrates a notable spike for drugs such as olanzapine, quetiapine, risperidone, and aripiprazole between 2011 and 2013, followed by a partial decline, stabilizing to some extent by 2021 (▶ **Fig. 3**).

▶ **Table 1** presents the basic demographic characteristics and AP treatment details for the subjects in our analysis, covering data on prescriptions, gender distribution, age specifics, and treatment persistence across FGA and SGA classes. From January 1, 2001, to December 31, 2021, among 3,300,817 SSN beneficiaries aged 18-65, we identified 45,857 individuals with an average age of 43.4 years (SD 12.2) who received at least three dispensations of one of the analyzed APs without any prior consumption in the previous year (incident cases). Of these, 42,434 subjects (93 %) received at least two continuous prescriptions and were thus included in our study cohort. These subjects were responsible for generating a total of 58,232 prescription events that were used for comparative assessments. Among these, 90 % of the prescription events analyzed involved polypharmacy.

Comparisons between groups revealed statistically significant differences in terms of PDD and TTD, with $p < 0.001$ for all compar-



▶ **Fig. 2** 2001–2021 Antipsychotics (APs) Dispensation Prevalence: Annual dispensation of three or more APs (FGA = First Generation Antipsychotic; SGA = Second Generation Antipsychotic).



▶ **Fig. 3** 2001–2021 Antipsychotics (APs) Dispensation Incidence: Annual new dispensation of three or more APs (FGA = First Generation Antipsychotic; SGA = Second Generation Antipsychotic).

isons. Specifically, clozapine exhibited a longer TTD than all other APs, with a median TTD of 175 days (IQR: 77-518), demonstrating statistical significance in all comparisons ($p < 0.001$).

▶ **Table 1** shows that prescribed dosages of various APs are within recommended ranges; specifically, olanzapine, risperidone, aripiprazole, and amisulpride are on the higher end, clozapine, haloperidol, and quetiapine are intermediate, while FGAs are on the lower end.

Globally, 38 % of the prescription events were discontinued within 3 months of the initial prescription, and 80 % within 1 year. Within the first 12 months, only 0.4 % of those who discontinued resumed their original AP therapy, while 0.6 % started a different AP therapy. A substantial 99 % did not resume any new continuative AP treatment at 1-year. Over the extended period of the first 24 months, a slightly higher proportion resumed a new continuative AP treatment: 2 % returned to their original therapy and 4 % opted for a different AP. Nevertheless, a significant 94 % of the patients did not resume any new AP continuative therapy at 2 years. It should be noted that 87 % of the discontinuers were on AP polytherapy; thus, discontinuing the AP medication started 3 months earlier did not imply a complete cessation of AP therapy. Among discontinuers, both polytherapy and monotherapy groups showed virtually identical AP therapy resumption rates (i. e., 1 % at 1 year and 6 % at 2 years), suggesting that the therapy modality does not significantly influence whether patients resume a new continuative treatment after discontinuation. Notably, among all discontinuers, 12 %—specifically those in monotherapy who did not resume any AP medications—were found not to be on continuous AP therapy within 2 years. Meanwhile, 88 % were, in fact, continuing with an AP therapy, either because they were initially on polytherapy or because they had started a different treatment.

▶ **Fig. 4**, illustrates the age- and sex-adjusted survival function estimates over a 365-day period for FGAs and SGAs. It shows a greater persistence in treatment for SGAs compared to FGAs, with this disparity being particularly evident by the 90-day primary endpoint.

▶ **Fig. 5** illustrates the age- and sex-adjusted survival function estimates for various APs at 3 months. It visually highlights marked differences in treatment persistence by the 90-day primary endpoint: clozapine exhibits the highest persistence of use, indicating a lower discontinuation rate compared to all other drugs; haloperidol and quetiapine show a more marked decrease in persistence, suggesting higher discontinuation rates among patients.

In ▶ **Fig. 6**, we present the age- and sex-adjusted hazard ratios (HRs) for a set of 28 AP comparisons based on the TTD at the 3-months. The results demonstrate 24 significant differences. As a class, SGAs demonstrated better treatment persistence than FGAs. Furthermore, all six SGAs have HRs indicating superior persistence when compared to the class of FGAs. Clozapine stands out for its superior persistence, surpassing the other five SGAs: olanzapine, aripiprazole, amisulpride, risperidone, and quetiapine. Olanzapine and aripiprazole trailed behind it, yet still showed better results than both risperidone and quetiapine. Both amisulpride and risperidone performed only better than quetiapine. Notably, quetiapine seems to be at a disadvantage, as it was inferior in terms of 3-month treatment discontinuation in all its pairwise comparisons against other SGAs.

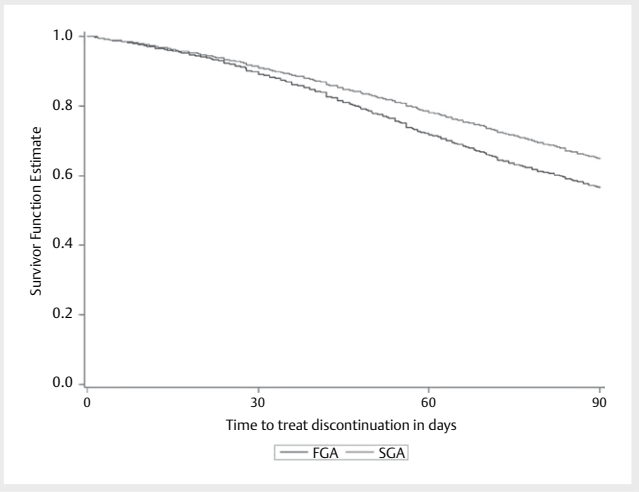
Further adjustments for polypharmacy and year yielded unwavering outcomes (see ▶ **Table 2**).

In our secondary analyses, we further evaluated the long-term persistence of AP treatments by comparing HRs for time-to-treatment discontinuation across several time frames, from 0–2 years to 0-20 years. Additionally, we illustrated the long-term time-to-treatment discontinuation over a 0-20-year period through survival graphs, providing a visual representation of treatment persistence across the studied APs (**Supplementary Figure S1–S3**). Notably, the head-to-head comparisons of APs showed general consistency in their HRs over time, particularly confirming clozapine's superiority across all periods (**Supplementary Table**

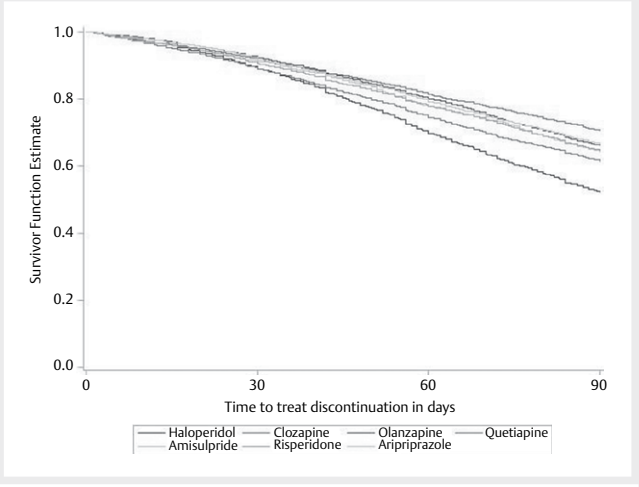
▶ **Table 1** Demographics and antipsychotic treatment data of patients included in this study (Study Cohort Subjects n = 42,434). AP: antipsychotic; FGA: first-generation antipsychotic; SGA: second-generation antipsychotics; SD: standard deviation.

	Haloperidol	Clozapine	Olanzapine	Quetiapine	Amisulpride	Risperidone	Aripriprazole	FGA*	SGA*
Incident Prescriptions, n	5210	3120	17446	16289	1541	7611	8879	12028	40112
Females, n (%)	2340 (44.91%)	1115 (35.74%)	8111 (46.5%)	8750 (53.7%)	585 (38.0%)	2984 (39.2%)	4684 (52.8%)	5575 (46.4%)	19409 (48.4%)
Age, mean (SD)	44.3 (11.5)	39.8 (11.6)	43.3 (12.3)	45.4 (12.3)	44.4 (11.6)	41.7 (12.4)	40.6 (12.4)	44.30 (11.6)	42.9 (12.8)
18–34 years, n (%)	1133 (21.8%)	1118 (35.8%)	4616 (26.5%)	3418 (21.0%)	333 (21.6%)	2332 (30.6%)	2884 (32.5%)	2616 (21.8%)	11287 (28.1%)
35–64 years, n (%)	4077 (78.3%)	2002 (64.2%)	12830 (73.5%)	12871 (79.0%)	1208 (78.4%)	5279 (69.4%)	5995 (67.5%)	9412 (78.3%)	28825 (71.9%)
Study cohort: continuative Prescriptions, n (%)	4441 (85.2%)	2852 (91.4%)	16601 (95.2%)	14322 (87.9%)	1383 (89.8%)	6788 (89.2%)	8285 (93.3%)	8001 (66.5%)	39572 (98.7%)
Females, n (%)	1939 (43.7%)	1002 (35.1%)	7683 (46.3%)	7678 (53.6%)	532 (38.5%)	2645 (39.0%)	4379 (52.9%)	3670 (45.9%)	18910 (47.8%)
Age, mean (SD)	44.1 (11.5)	39.5 (11.6)	43.2 (12.3)	45.2 (12.3)	44.2 (11.5)	41.6 (12.4)	40.5 (12.4)	44.2 (11.5)	42.5 (12.8)
18–34 years, n (%)	992 (22.3%)	1047 (36.7%)	4416 (26.6%)	3085 (21.5%)	301 (21.8%)	2095 (30.7%)	2714 (32.8%)	1751 (21.9%)	11510 (29.1%)
35–64 years, n (%)	3449 (77.7%)	1805 (63.3%)	12185 (73.4%)	11237 (78.5%)	1082 (78.2%)	4693 (69.1%)	5571 (67.2%)	6250 (78.1%)	28062 (70.9%)
Time to treatment discontinuation, mean (SD)	171.5 (306.5)	517.8 (998.3)	248.4 (627.0)	372.1 (1938.1)	338.5 (1823.7)	261.0 (991.9)	337.8 (1439.1)	751.5 (3224.9)	589.3 (2949.2)
Time to treatment discontinuation (TTD), median (IQR)	92 (53–171)	175 (77–518)	128 (70–241)	121 (58–268)	120 (66–216)	127 (66–229)	133 (69–254)	103 (54–210)	128 (66–257)
Personalised daily dose (PDD), median (IQR)	5.2 (3.33–9.4)	266.6 (155.5–466.5)	10.8 (6.7–20.0)	206.9 (68.4–514.3)	428.6 (260.9–857.1)	4.9 (3.2–8.9)	15.6 (9.7–28.0)	–	–
Chlorpromazine equivalent PDD, median (IQR)	313 (200–562.5)	399.9 (233.3–699.8)	323 (200–600)	165.5 (54.7–411.4)	195.7 (150.0–321.4)	461.5 (292.7–857.1)	311.1 (193.0–560.0)	117.7 (46.5–304.1)	300.0 (155.6–589.5)
Olanzapine equivalent PDD, median (IQR)	6.5 (4.2–11.7)	8.9 (5.2–15.6)	10.8 (6.7–20.0)	5.2 (1.7–12.7)	10.7 (6.5–21.4)	10.9 (7.1–20.0)	10.4 (6.43–18.7)	3.9 (1.6–10.1)	8.75 (4.9–16.7)
0–3 months AP polypharmacy prescriptions, n (%)	3735 (84.1)	2689 (94.3)	15447 (93.1)	12924 (90.2)	1290 (93.3)	6274 (92.4)	7427 (89.6)	6125 (76.6)	37175 (93.9)
0–3 months Number of AP polipharmacy drugs, median (IQR)	1 (1–2)	1 (1–2)	1 (1–1)	1 (1–1)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–1)	1 (1–1)
0–2 years AP polypharmacy prescriptions, n (%)	3787 (85.3)	2707 (94.9)	15490 (93.3)	12941 (90.4)	1292 (93.4)	6284 (92.6)	7434 (89.7)	6131 (76.6)	37098 (93.8)
3–5 years AP polypharmacy prescriptions, n (%)	175 (91.1)	594 (93.8)	1021 (89.0)	1062 (76.4)	62 (82.7)	311 (84.3)	527 (82.2)	356 (53.1)	2368 (68.1)
6–20 years AP polypharmacy prescriptions, n (%)	29 (85.3)	194 (92.4)	208 (87.4)	243 (62.0)	13 (54.2)	59 (67.8)	104 (67.1)	59 (18.1)	494 (39.1)

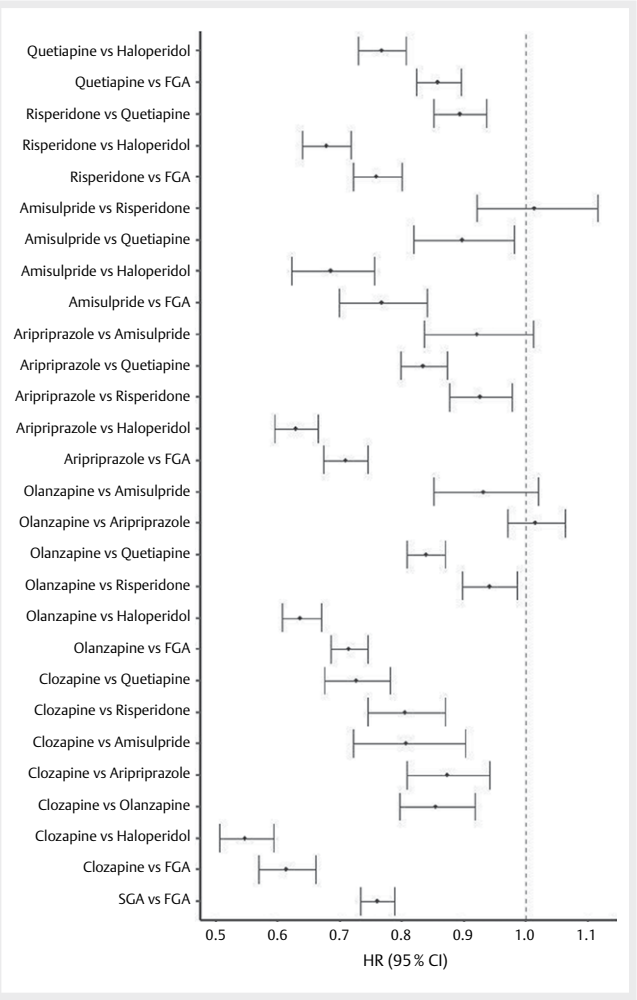
*Only the first continuous prescribing event for each subject within the same class was included. This accounts for the lower total counts of SGA and FGA compared to the sum of individual drugs within these classes.



▶ **Fig. 4** Age and Sex-Adjusted Kaplan-Meier Survival Curves for Time to Treatment Discontinuation by Antipsychotic Class: First-Generation Antipsychotics (FGA) vs. Second-Generation Antipsychotics (SGA).



▶ **Fig. 5** Age and Sex-Adjusted Kaplan-Meier Survival Curves for Time to Treatment Discontinuation by Antipsychotic.



▶ **Fig. 6** Age and Sex-Adjusted Hazard Ratios (HRs) and Their 95 % Confidence Intervals (CIs) for 3-Month Time-to-Treatment Discontinuation Across Various Antipsychotics. Note: CIs entirely to the left of the dashed line indicate superior effectiveness of the first compared drug.

S1). However, some variations were observed, especially in the case of quetiapine. Secondary analyses showed an inversion of trends in its favor, outperforming olanzapine, risperidone, and amisulpride, despite being inferior to them in the primary analysis.

Discussion

From 2001 to 2021, SGA prescriptions increased over FGAs, possibly due to perceived better effectiveness and tolerability. Although the general trend for SGAs was upward, specific drugs like olanzapine showed significant fluctuations, likely influenced by external factors. Initially approved for schizophrenia, olanzapine received expanded approvals for manic episodes and bipolar disorders in the early 2000s, broadening its applications. However, in 2006, lawsuits over its metabolic side effects impacted global prescription trends, including in Italy [38]. This decline reversed around 2012 when olanzapine's patent expired, leading to increased prescriptions with the availability of cheaper generics—a trend also seen with risperidone and quetiapine. By 2021, the rise in SGA prescriptions, notably quetiapine and olanzapine, may have been influenced by the mental health challenges of the COVID-19 pandemic.

We studied the persistence of newly initiated AP treatments in a naturalistic setting where 90 % of subjects were on polytherapy during the first 3 months of therapy, highlighting challenges associated with monotherapy and underscoring the need for personalized strategies. One possible explanation for this high polypharmacy rate is tapering practices, where patients are gradually transitioned from one AP to another. However, polypharmacy remained consistently high during longer treatment periods, particularly within the first 5 years, with a subsequent reduction only during the 6–20-year follow-up, likely reflecting natural attrition. This trend of later

▶ **Table 2** Comparative 3-month antipsychotics treatment discontinuation rates: Unadjusted hazard ratios (HRs), adjusted hazard ratios (HRad) for age, sex, polypharmacy, and period/year of study entry, and their 95 % confidence intervals (CIs).

		HRs (CIs)	Age and sex HRad (CIs)	Age,sex, and politherapy HRad (CIs)	age, sex, and period HRad (CIs)
Clozapine vs.	Haloperidol	0.54 (0.50; 0.59)	0.55 (0.51; 0.59)	0.55 (0.51; 0.60)	0.55 (0.51; 0.60)
	Olanzapine	0.85 (0.79; 0.91)	0.85 (0.79; 0.92)	0.86 (0.80; 0.92)	0.85 (0.79; 0.92)
	Quetiapine	0.71 (0.66; 0.76)	0.73 (0.68; 0.78)	0.73 (0.68; 0.79)	0.73 (0.68; 0.78)
	Amisulpride	0.80 (0.71; 0.89)	0.81 (0.72; 0.90)	0.81 (0.72; 0.90)	0.81 (0.72; 0.90)
	Risperidone	0.80 (0.74; 0.87)	0.80 (0.74; 0.87)	0.80 (0.74; 0.87)	0.80 (0.74; 0.87)
	Aripriprazole	0.86 (0.79; 0.92)	0.87 (0.81; 0.94)	0.88 (0.81; 0.95)	0.90 (0.83; 0.97)
	FGA	0.61 (0.57; 0.66)	0.61 (0.57; 0.66)	0.65 (0.60; 0.70)	0.62 (0.57; 0.66)
Olanzapine vs.	Haloperidol	0.64 (0.61; 0.67)	0.64 (0.61; 0.67)	0.63 (0.60; 0.66)	0.64 (0.61; 0.67)
	Quetiapine	0.83 (0.80; 0.87)	0.84 (0.81; 0.87)	0.84 (0.81; 0.87)	0.84 (0.81; 0.87)
	Amisulpride	0.94 (0.86; 1.03)	0.93 (0.85; 1.02)	0.93 (0.85; 1.02)	0.93 (0.85; 1.02)
	Risperidone	0.94 (0.90; 0.99)	0.94 (0.90; 0.99)	0.94 (0.90; 0.99)	0.94 (0.90; 0.99)
	Aripriprazole	1.01 (0.96; 1.05)	1.01 (0.97; 1.06)	1.01 (0.97; 1.06)	1.02 (0.98; 1.07)
	FGA	0.71 (0.69; 0.75)	0.71 (0.68; 0.74)	0.72 (0.69; 0.75)	0.72 (0.69; 0.75)
Quetiapine vs.	Haloperidol	0.77 (0.73; 0.81)	0.77 (0.73; 0.81)	0.76 (0.73; 0.80)	0.77 (0.73; 0.81)
	FGA	0.86 (0.83; 0.90)	0.86 (0.82; 0.89)	0.87 (0.83; 0.91)	0.87 (0.83; 0.90)
Amisulpride vs.	Haloperidol	0.68 (0.62; 0.75)	0.69 (0.62; 0.75)	0.69 (0.63; 0.76)	0.69 (0.63; 0.77)
	Quetiapine	0.89 (0.81; 0.98)	0.90 (0.82; 0.98)	0.90 (0.82; 0.99)	0.90 (0.82; 0.99)
	Risperidone	1.01 (0.92; 1.11)	1.01 (0.92; 1.12)	1.01 (0.92; 1.11)	1.01 (0.92; 1.12)
	FGA	0.76 (0.70; 0.84)	0.77 (0.70; 0.84)	0.81 (0.74; 0.89)	0.77 (0.70; 0.85)
Risperidone vs.	Haloperidol	0.68 (0.64; 0.72)	0.68 (0.64; 0.72)	0.68 (0.64; 0.72)	0.69 (0.65; 0.73)
	Quetiapine	0.89 (0.84; 0.93)	0.89 (0.85; 0.94)	0.89 (0.85; 0.94)	0.89 (0.85; 0.94)
	FGA	0.76 (0.72; 0.80)	0.76 (0.72; 0.80)	0.78 (0.74; 0.82)	0.76 (0.73; 0.80)
Aripriprazole vs-	Haloperidol	0.64 (0.60; 0.67)	0.63 (0.59; 0.66)	0.63 (0.59; 0.66)	0.63 (0.60; 0.67)
	Quetiapine	0.83 (0.79; 0.87)	0.83 (0.80; 0.87)	0.84 (0.80; 0.87)	0.83 (0.79; 0.87)
	Amisulpride	0.93 (0.85; 1.02)	0.92 (0.84; 1.01)	0.92 (0.83; 1.01)	0.88 (0.79; 0.97)
	Risperidone	0.94 (0.89; 0.99)	0.93 (0.88; 0.98)	0.93 (0.88; 0.98)	0.92 (0.87; 0.97)
	FGA	0.71 (0.68; 0.75)	0.71 (0.67; 0.74)	0.73 (0.69; 0.76)	0.72 (0.68; 0.76)
SGA vs-	FGA	0.76 (0.73; 0.79)	0.76 (0.73; 0.79)	0.77 (0.74; 0.80)	0.76 (0.73; 0.79)

FGA: first-generation antipsychotics; SGA = Second-generation antipsychotic.

polypharmacy reduction was more pronounced for SGAs, suggesting a shift in treatment strategies over time.

Our primary findings, consistent across therapy types even after adjusting for polytherapy, confirm the superiority of SGAs over FGAs and, specifically, the persistence of clozapine. Notable disparities in drug persistence evident at the 90-day endpoint persisted and remained stable over the following years.

To analyze the persistence of the classes of FGAs and SGAs, we used a method that considers intra-class switching, where transitions between different antipsychoticAPs within the same class are not classified as treatment discontinuations. This approach led to particularly prolonged TTD for the class of FGAs. Despite this, our analysis still highlights the clear superiority of SGAs over FGAs. The superiority of SGAs aligns with the insights drawn from experimental research [8–12]. In particular, this reaffirms the narrative presented by Leucht et al. and Huhn et al., which emphasized the superior performance of certain SGAs, specifically clozapine, amisulpride, olanzapine, and risperidone [8–10]. Moreover, the finding of the superiority of clozapine is in line with the results reported by Kishimoto et al., highlighting its dominance among other SGAs in terms of all-cause discontinuation [11, 12].

The mixed results for other SGAs, especially quetiapine's limited persistence compared to counterparts like clozapine, olanzapine, and risperidone, require further exploration. This aligns with Leucht et al. (2013) who found quetiapine moderately effective and noted higher discontinuation rates in 2009 [9, 39]. However, in our secondary analyses (Supplementary Materials), quetiapine demonstrated higher persistence over longer follow-up periods (up to 20 years) compared to other APs except clozapine, contrasting with the primary endpoint. This suggests that quetiapine may have a more favorable profile in long-term treatment strategies. Nonetheless, the value of these secondary results is limited by the decreasing number of subjects who continue taking the same medication over extended follow-up periods, reducing the absolute number of individuals at risk and making the comparisons less representative.

Conversely, while olanzapine often leads in experimental studies, our data presents a more complex view. Similarly, amisulpride

and risperidone, typically praised for their efficacy, showed inconclusive results in our study [8–12]. Our findings highlight clozapine's marked persistence over olanzapine, consistent with previous observational studies. Meta-analyses by Soares-Weiser et al. (2013) and Masuda et al. (2019) have reported similar outcomes [40, 41]. Weiser et al. (2021) noted that American veterans faced a significantly lower risk of discontinuing clozapine compared to olanzapine [42]. Furthermore, a comprehensive 7-year retrospective study in Québec found that individuals on risperidone, clozapine, or polytherapy were significantly less likely to discontinue treatment than those on olanzapine and quetiapine [43]. Additionally, Brodeur et al. (2022) observed an exceptionally low discontinuation risk with clozapine compared to olanzapine [44]. These consistent findings affirm the pivotal role of clozapine in managing schizophrenia, underscoring its efficacy and broad applicability across diverse patient populations. However, the notable superiority of clozapine over olanzapine in our study, echoed in other observational research, contrasts with results from meta-analyses of RCTs. This discrepancy likely stems from clozapine being prescribed specifically for treatment-resistant schizophrenia, where it demonstrates superior efficacy compared to other APs, which are more likely to be prescribed for a broader range of conditions in naturalistic settings as their prescribability has steadily increased [45].

Our study, inherent with biases typical of observational designs such as selection bias, endpoint misclassification, and confounding, is further limited by the absence of psychiatric diagnoses and other clinical details. This gap prevents us from assessing the appropriateness of AP prescriptions or distinguishing between patients with conditions like psychosis, treatment-resistant depression, or bipolar disorders. For example, the lower persistence observed with quetiapine may reflect its adjunctive role in managing conditions such as anxiety or insomnia, often at doses lower than those used for primary AP purposes, thereby influencing its 3-month TTD rates. To mitigate bias from diagnostic variability, we focused our analysis on adults aged 18-65 years, excluding those prescribed APs for dementia-related behaviors, thus aiming for a more uniformly diagnosed cohort.

Utilizing observational data to infer drug effectiveness poses challenges, as the endpoint of treatment discontinuation may not fully capture patient experiences. For instance, discontinuations could indicate recovery or symptom control, not merely treatment failure. Without detailed reasons for each cessation, we risk misinterpreting positive outcomes as ineffective treatment. External factors like patient beliefs or inadequate support could also drive discontinuations. To minimize this bias, our study focused on a 3-month treatment duration, aligning with the acute phase of AP treatment, which typically isn't long enough to observe discontinuations due to recovery.

While our research design has known limitations, its significance remains robust. Our large-scale epidemiological study enhances the understanding of drug efficacy in routine clinical practice, not just in controlled environments. Additionally, the high prevalence of polytherapy in our findings underscores the complexities and criticalities of real-world AP prescribing [46]. The early predictive value of treatment discontinuation as a reliable indicator of long-term effectiveness, highlights the utility of observational data in clinical decision-making and research. Furthermore, the stability of our findings, unaffected by annual prescription trends, emphasizes the reliability of our method in evaluating pharmacological outcomes.

Despite the inevitable limitations of its observational design, the extensive two-decade span of our study provides valuable insights for advancing AP research. It bolsters the existing literature on the superiority of SGAs over FGAs and highlights clozapine as a treatment option with the highest persistence rates [47, 48].

These findings have important implications for clinical decisions and could guide future research into broader applications and management strategies for clozapine. Highly effective for treatment-resistant schizophrenia, clozapine offers benefits including reduced suicide risk and improved cognitive function, thereby enhancing quality of life. However, its usage is constrained by the need for strict monitoring due to serious side effects such as agranulocytosis and myocarditis [45]. Although clozapine showed superior persistence in our study, it remained one of the least prescribed APs. Our findings underscore the need for further RCTs to compare clozapine with other APs, such as olanzapine, across various diagnoses, while also exploring innovative strategies for its utilization, management of potential side effects, and addressing polypharmacy considerations. This could extend its benefits while optimizing its monitoring for safer, broader applications.

Contributors

Alberto Parabiaghi formulated and wrote the study protocol, including the methodology, and led the development of the project. Barbara D'Avanzo, and Angelo Barbato contributed to the conception of the study and supervised the development of the project. Alessia Galbussera was responsible for data management and conducted the statistical analysis. Mauro Tettamanti oversaw the statistical analysis. Alberto Parabiaghi led the interpretation of the data. The original draft was written by Alberto Parabiaghi. Angelo Barbato and Barbara D'Avanzo contributed to the results validation. All authors reviewed the drafted work and approved the final manuscript.

Data availability

Study data were obtained from the Lombardy Region under specific restrictions. These data, used under a license for the current study, are not publicly accessible. Access was regulated through the EPIFARM agreement between the Istituto di Ricerche Farmacologiche "Mario Negri" IRCCS and the Regional Health Authority, with the authorization granted by the latter. However, data can be made available by the authors upon reasonable request and with the Lombardy Region's permission. Additional details on the results are also available from the corresponding author upon reasonable request.

Informed Consent Statement

All methods were carried out in accordance with the Declaration of Helsinki. The study was exempt from patients informed consent, and it was waived according to General Authorization for the Processing of Personal Data for Scientific Research Purposes Issued by the Italian Privacy Authority on August 10, 2018; https://www.garantepri-

vacy.it/home/docweb/-/docweb-display/docweb/9124510#5. Furthermore, the study provided sufficient guarantees of individual records anonymity, with respect to Italian privacy law.

Conflict of interest

The authors declare that they have no competing interests.

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