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Long-Term Utilization Patterns of Antidepressants in Two Italian Regions: A Naturalistic Observation of Over 2 Million Individuals Across 5 Years

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ABSTRACT

Background: Antidepressant drugs (AD) are commonly used and prescribed. However, factors associated with their prescription and use have not yet been fully characterized.

Objective: To better characterize long-term utilization patterns of antidepressants, leverage data collected by naturalistic observation (i.e., routinely collected administrative prescription data, without experimental manipulation) across 5 years in two Italian regions.

Methods: Sociodemographic factors associated with prescription in a population of more than 2,000,000 individuals were explored (multivariate logistic regression). Multivariate survival analysis was employed to investigate factors associated with the time to drug discontinuation. Diverging patterns of use were described and empirically tested by logistic regression, performed on time series of drug utilization.

Results: A total of 219,351 incident users were observed. Older age and female sex were associated with a more likely prescription (age 45–64: incidence rate ratio [IRR] 1.63; age 65–84: IRR 3.266; age 85+: IRR 10.244; all $p<0.001$: females vs. males IRR 1.740, Z-score 50.08, $p<0.001$). Older age and the use of tricyclic or other antidepressants (compared to selective serotonin reuptake inhibitors [SSRIs]) were associated with lower discontinuation and thus longer treatment persistence (minimum hazard ratio [HR], 0.680, Z-score −36.08, $p<0.001$). Predictive models could identify diverging patterns of use (area under the curve [AUC] ≥0.697).

Conclusions: The long-term pharmacoutilization of antidepressants was shown to be under the influence of structural and sociodemographic factors. Considering the recent directive by the European Commission on the European Health Data Space, implications for public health policies and future research may be considered.

1 | Background

Antidepressant drugs (AD) are approved for the treatment of a wide range of psychiatric conditions, such as major depression, generalized anxiety disorder, panic disorder, obsessive compulsive disorder, posttraumatic stress disorder, and bulimia nervosa [1]. These conditions significantly impact the quality of life of sufferers and remarkably contribute to the overall burden of disease and/or disability across the general population at the epidemiological level [2, 3].

For instance, current epidemiological estimates of depressive disorders describe these disorders as the third and fifth leading causes at the global level of years of living with disability (YLD) for women and men, respectively [4]. The access to psychiatric care has been shown to be influenced by social factors, such as the perceived stigma towards mental health [5, 6]. Other social determinants of health may influence access and utilization of psychiatric care, including cultural stances towards mental distress, thus possibly also impacting adherence to treatment [7, 8].

The National Institute for Health and Care Excellence (NICE), through its guidelines, generally recommends that ADs should be continued for 6 months after symptoms remission and then maintained for a maximum of 2 years, except for people at high risk of relapse or those with very severe or treatment-resistant depressive episodes [1]. This approach allows to first treat the acute phase of the disorder and then stabilize the patient in the long term. Similar treatment patterns are recommended for generalized anxiety [9], panic or post-traumatic disorders [1]. Nonetheless, several patients might interrupt the assumption of ADs due to concerns about side effects, believing to have already been healed, or perceiving an offset in the balance between risk/benefit relative to long-term use [10].

An open question in the current literature is whether short- and long-term utilization patterns might differ and whether this difference might be influenced by age, sex, or sociocultural factors [11]. Additionally, a long-term perspective could inform public policymakers about underlying patterns within the general population, as well as better characterizing the role of environmental characteristics as influencing chronic utilization [12].

These results might represent a novel target for public health interventions and health-education campaigns, especially when considering how the information space could aid public policymakers in a digitalized framework of action [13]. The current work will propose a simplified method to monitor, track, and compare long-term drug utilization patterns across two large reference populations. Doing so, it will establish a proof-of-concept for future technical advancements in public health. In particular, the novelty of the present study in comparison to the current literature relies on (i) its long-term follow-up (5 years), (ii) the use of trajectory clustering approaches to reach a more granular characterization of AD use not captured by summary statistics alone, and (iii) a simultaneous cross-regional comparison to isolate regional variations, controlling for national-level regulatory and reimbursement factors.

1.1 | Aims

The primary aim of the current study was to describe the long-term utilization pattern for ADs across two large reference populations in Italy, namely one pertaining to the metropolitan area of Florence, Tuscany, and one pertaining to the catchment area of the metropolitan area of Bologna, Emilia-Romagna. The secondary aim of the study was to investigate the role of structural (regional) and sociodemographic factors on pharmacoutilization and retention.

2 | Methods

2.1 | Data Source

The National Healthcare Service (SSN) in Italy is tax-based and is organized across three levels: national, regional, and local. In summary, the Italian SSN partially mirrors the United Kingdom for what concerns the organization of its National Health Service (NHS). The Italian SSN was established 20 years after the NHS and also follows the Beveridge model of universal coverage and single payer, with a focus on primary care. Regions manage and finance healthcare services. Local Health Authorities (LHA), directly organize territorial services. LHAs reimburse and account for all expenses related to healthcare services dispensed to residents in their catchment area.

The current study is based on the analysis of the administrative databases from two large LHAs in central Italy: the LHA of the metropolitan area of Florence, Tuscany (encompassing the metropolitan conglomerate of three cities: Florence, Pistoia, and Prato) and the LHA of the metropolitan area of Bologna, Emilia-Romagna. These two LHAs were used as proxies of the Tuscany and Emilia Romagna regions, respectively, while levering out potential divergences due to rural/urban distributions (as both center Tuscany and Bologna LHAs are highly urbanized, metropolitan areas).

For each subject in the database, demographic information was linked with pharmaceutical claim records by using anonymized codes. The following data points were retrieved: date of dispensing by the local pharmacy for ADs, active substance prescribed and its anatomical therapeutic chemical code (ATC classification system). Only dispensing classified as N06A* (ADs) according to the ATC classification systems were included in the analysis. Across N06A*, active substances were classified as non-selective monoamine reuptake inhibitors (tricyclics, N06AA*), selective serotonin reuptake inhibitors (SSRIs, N06AB*), and other ADs (e.g., Bupropion, Trazodone).

2.2 | Study Design and Population

The current study was descriptive and retrospective. The source population was composed of all residents in the LHA aged 18+ between 2009 and 2013. All subjects with at least one dispensing of AD from January 2009 to December 2013 were retrieved from the databases of LHA of Florence and Bologna, and the date of the first dispensing was considered the index date. Patients with at least one dispensing of AD and none in the prior 5 years were considered incident users. Each incident user was followed up for 5 years after the first dispensing. The 5 years were divided into 20 trimesters, and for each of them, the presence of at least one dispensing of AD was assessed. For each study subject, a latent pattern of use was described according to a semi-supervised clustering algorithm (see below, Section 2.3 for further details).

2.3 | Statistical Analysis

The source population was identified from the LHA registry and described per gender and age band (18–44, 45–64, 65–84, and 85+). These age categories were selected based on clinical and epidemiological relevance, reflecting distinct life stages associated with differing patterns of psychiatric morbidity and healthcare utilization, and are consistent with those adopted in prior studies conducted on electronic health records [14–16]. The boundaries also correspond to thresholds frequently used in Italian administrative health data research and national epidemiological surveillance. The number of users was calculated. Frequency distribution of sociodemographic variables (LHA, age, and sex) and class of AD at index date were described both in the cohort of incident users and in the cohort of incident users with at least 5 years of follow-up. The yearly gender- and age-band-specific incidence of use was calculated by dividing the number of new users per year by the number of persons in the source population, minus the number of non-incident users. Incidence rate ratios (IRRs) were thus derived to model rates of first prescription events across the source population.

The association between covariates of interest (age, sex, and LHA of residence) and incidence was estimated by using a generalized multivariate regression model, assuming an underlying Poisson distribution, with corresponding 95% confidence intervals (95% CIs).

The time to discontinuation of AD was identified in the cohort, and a survival analysis was conducted by fitting a Cox model using LHA, gender, age band, and first AD as covariates. Hazard ratios (HRs) below 1 indicate a lower hazard of discontinuation, reflecting longer treatment persistence, while HRs above 1 indicate a shorter time to discontinuation.

In the cohort of incident users with at least 5 years of follow-up, the trajectory of dispensing across 20 trimesters was identified. Trajectories were clustered by predefined criteria, according to expert consensus:

a. Subjects with a first discontinuation (i.e., without dispensing in the second trimester)
    1. With no further dispensing ($N = 67{,}296$, 37, 7%)
    2. With subsequent dispensing, but never in two consecutive trimesters ($N = 20{,}570$, 11, 5%)
    3. With subsequent dispensing in two or more consecutive trimesters ($N = 26{,}118$, 14, 6%)
b. Subjects who did have a dispensation in the second trimester
    4. With dispensing up to a maximum of 2 years ($N = 16{,}295$, 9, 1%)
    5. With dispensing beyond 2 years, with at least one discontinuation before the end of the 2 years ($N = 31{,}673$, 17, 7%)
    6. With continuous use between two and 5 years ($N = 9344$, 5, 2%)
    7. With continuous use for 5 years ($N = 7330$, 4, 1%)

The frequency of people in each cluster with at least one AD dispensing in each month was represented graphically. See Figure S1 for a graphical representation of cluster trajectories.

To assess the validity of the clustering analysis, a series of logistic regressions were performed. These logistic regressions used the time series of drug dispensing in order to predict cluster identity. Specifically, seven logistic models were fitted to compare differences in age, gender, and first AD used among subjects belonging to the single cluster versus all the others. The area under the curve (AUC) was used to check the model's performance. AUC represents the degree or measure of separability. It tells how much the model is capable of distinguishing between classes. The higher the AUC, the better the logistic models fit.

To better explore the pattern of use within each cluster, Sankey plots were adopted. This type of graphical tool highlights the change from one state to another over time, where the width of the flow is proportional to the percentage of subjects. We considered the state as the presence (or absence) of AD dispensing, and the follow-up was divided into 20 trimesters as previously described.

All analyses were performed by using R (version 4.3.1) [17] and STATA 17 statistical software.

2.4 | Ethical Approval

The study was conducted as part of the activity plan of the Tuscan Regional Healthcare Agency (ARS Toscana), which is approved by its board, and participated in by the Regional Council of Tuscany, Italy.

3 | Results

The total population of the two catchment areas accounted for 2,192,095 individuals ($N = 1{,}456{,}009$ and 736,086 for LHA Florence and LHA Bologna, respectively). The gender and age distribution were comparable between the two catchment areas, with the reference population being mainly above 45 years of age (age below 45 years old, 38.0%, above 45 years old, 62.0%) and with a slight bias towards women (gender 52.8% women vs. 47.2% men). In the source population, 455,579 patients with at least one dispensing of AD were observed. See Tables 1 and 2 for further details.

3.1 | Factors Associated With AD Prescription

Among users, a total of 219,351 incident users (persons who had been living in their LHA for at least 5 years and had no previous dispensing during such period) were identified (149,285 from Florence and 70,066 from Bologna). Table S1 describes the characteristics of the population of incident users.

The incidence of AD use within the two LHA was significantly associated with both structural and sociodemographic factors. In fact, individuals within the LHA Florence catchment area were more likely to be prescribed an AD (Incidence rate ratio–IRR 1.357, Z-score 27.59, $p < 0.001$). Higher age was associated with a higher likelihood of AD prescription, progressively increasing according to age categories (age 45–64: IRR 1.63; age 65–84: IRR 3.266; age 85+: IRR 10.244; all $p < 0.001$). Females were more likely to be prescribed an AD in comparison to males (IRR 1.740, Z-score 50.08, $p < 0.001$).

TABLE 1 | Descriptive statistics, study population in catchment areas.

Variable	Category	LHA Florence	LHA Bologna	Total
N		1,456,009 (66.42%)	736,086 (32.58%)	2,192,095 (100%)
Gender	Men (%)	685,591 (47.1%)	348,727 (47.4%)	1,034,318 (47.2%)
	Women (%)	770,418 (52.9%)	387,359 (52.6%)	1,157,777 (52.8%)
Age class	18–44 (%)	542,551 (37.3%)	289,493 (39.3%)	832,044 (38.0%)
	45–64 (%)	476,855 (32.8%)	240,468 (32.7%)	717,323 (32.7%)
	65–84 (%)	350,872 (24.1%)	172,691 (23.5%)	523,563 (23.9%)
	85+ (%)	85,731 (5.9%)	33,434 (4.5%)	119,165 (5.4%)

Note: Overall characteristics of catchment areas.
Abbreviation: LHA, local health authority.

TABLE 2 | Descriptive statistics, individuals with additional 5 years of follow-up.

Variable	Category	LHA Florence	LHA Bologna	Total
N		122,846	55,780	178,626
Women (%)		78,611 (64.0%)	36,191 (64.9%)	114,802 (64.3%)
Age	18–44	37,281 (30.3%)	15,654 (28.1%)	52,935 (29.6%)
	45–64	41,028 (33.4%)	19,340 (34.7%)	60,368 (33.8%)
	65–84	38,744 (31.5%)	17,974 (32.2%)	56,718 (31.8%)
	85+	5,793 (4.7%)	2,812 (5.0%)	8,605 (4.8%)
AD type	Tricyclic	8,336 (6.8%)	4,389 (7.9%)	12,725 (7.1%)
	SSRI	92,785 (75.5%)	40,272 (72.2%)	133,057 (74.5%)
	Other	21,725 (17.7%)	11,119 (19.9%)	32,844 (18.4%)
Year	2009	26,723 (21.8%)	12,283 (22.0%)	39,006 (21.8%)
	2010	25,379 (20.7%)	12,164 (21.8%)	37,543 (21.0%)
	2011	24,124 (19.6%)	11,018 (19.8%)	35,142 (19.7%)
	2012	22,842 (18.6%)	10,100 (18.1%)	32,942 (18.4%)
	2013	23,778 (19.4%)	10,215 (18.3%)	33,993 (19.0%)

Note: Characteristics at baseline of individuals with at least one prescription in the study period.
Abbreviations: AD, antidepressant; LHA, local health authority.

A significant interaction between age and gender was observed, with older females being less likely to be prescribed an AD in comparison to older males (age 65–84: IRR 0.853; age 85+: 0.593; all $p < 0.001$). A significant interaction between age and city was also observed. In fact, in LHA Florence, the increase of incidence with older age was less marked when compared with LHA Bologna (age 45–64: IRR 0.813, age 65–84 IRR 0.820, age 85+ IRR 0.437, all $p < 0.001$). This result implies that even people initiating AD were younger in LHA Florence as compared to LHA Bologna; differences between LHAs were attenuated with increasing age. See Table S2 for further results.

3.2 | Factors Associated With Time to Discontinuation

Among the above-described incident users, 178,626 (81.4%) had an additional 5 years of follow-up, 122,846 (82.3%) being from Florence and 55,780 (79.6%) being from Bologna (see Table 2 for further details). Older age and the use of tricyclic or other ADs (vs. SSRIs) were associated with significantly longer treatment persistence (lower hazard of discontinuation), following a monotonically increasing pattern across age categories (HR 0.932 for age 45–64; HR 0.752 for age 65–84; HR 0.690 for age 85+; all $p < 0.001$), consistent with a significant trend toward greater persistence with advancing age. By contrast, gender and LHA were not significantly related to drug discontinuation. See Table 3 for further details.

3.3 | Subtypes of AD Use

To explore the validity of the semi-supervised clustering performed, a series of logistic regressions were performed. These logistic regressions used the time-series of drug dispensing in order to predict cluster identity. Moderate to high accuracy was achieved for each cluster (minimum AUC 0.697, maximum 0.917, Table 4). This result can be interpreted as a confirmation of low temporal heterogeneity within each cluster, thus providing preliminary

TABLE 3 | Multivariate survival analysis.

Variable	Hazard ratio	Standard error	*Z*-score	*p*-Value	95% confidence interval	
LHA: Florence vs. Bologna	0.963	0.005	−7.21	<0.001	0.953	0.973
Age: 45–64 vs. <45 years old	0.932	0.006	−11.67	<0.001	0.920	0.943
Age: 65–84 vs. <45 years old	0.752	0.004	−45.77	<0.001	0.743	0.761
Age: >85 vs. <45 years old	0.690	0.008	−30.46	<0.001	0.674	0.707
Gender: Women vs. Men	0.997	0.005	−0.57	0.569	0.987	0.999
Tricyclic AD	0.712	0.007	−36.28	<0.001	0.699	0.725
Other AD	0.680	0.007	−36.08	<0.001	0.666	0.694

Note: Number of subjects 178,626. Chi-squared 4621.49. Reference categories: LHA Bologna (for regional comparison); age <45 years (for age categories); male sex (for gender); SSRI (for antidepressant class). Hazard ratios below 1 indicate longer treatment persistence (lower hazard of discontinuation). Abbreviation: LHA, local health authority.

TABLE 4 | Validation of semi-supervised clustering, logistic regression performed on timeseries of drug utilization.

Cluster	Area under the curve
Cluster 2	0.697
Cluster 3	0.764
Cluster 4	0.771
Cluster 5	0.917
Cluster 6	0.862

Note: Cluster 1 and 7 were not reported, as the clusters of no further dispensation (Cluster 1) and continuous dispensation (Cluster 7) reached an AUC of 1.

support for the semi-supervised clustering definitions adopted in the study (Table S3 for more details on model coefficients).

To deeper explore the pattern of use within each cluster, Sankey plots were adopted. In Figure S2 we report five Sankey plots, corresponding to clusters from 2 to 6, visualizing timepoint by timepoint drug utilization patterns within each cluster.

In general, women belonging to our cohort discontinued less frequently, regardless of the LHA. Among the elderly, the portion of long-term users is higher, mainly in Florence. Moreover, the percentage of earlier time to interruption is higher among tricyclic users compared to the other two groups of AD. See Figure S3 for a graphical representation of the results.

Sociodemographic factors were also significantly associated with diverging clusters of interest. Tricyclic ADs were significantly associated with early discontinuation (Cluster 1), while SSRIs were with long-term retention (Cluster 4–7). Age was significantly and positively associated with long-term retention (Cluster 1, lower age vs. Cluster 4–7 older age—a higher proportion of >65-year-old individuals).

Structural factors were also significantly associated with drug retention and/or time to discontinuation. In fact, individuals in LHA Florence were more likely to be observed as exhibiting long-term drug utilization (Cluster 7).

In summary, distinct longitudinal patterns of utilization were empirically identifiable and associated with patient-level sociodemographic characteristics and regional origin. Older individuals, women, and SSRI users were characterized by longer treatment persistence, consistently across different analyses conducted.

4 | Discussion

This is the first study evaluating the naturalistic use of ADs in a population representative of the general population in two Italian regions over a 5-year timespan. According to the main findings, diverging patterns of prescriptions may emerge even in geographically adjacent regions. Moreover, these diverging patterns seem to be under the influence of sociodemographic factors, such as the age and sex of the specific patient. A second influence for the discrepancies in incidence of both prescription and DDD for ADs between the two LHAs here examined could be related to historical factors. Indeed, a pharmacoutilization study carried out in the mid-1990s already showed that Tuscany was in second place in Italy for the consumption of ADs [18].

The observed differences between catchment areas may reflect a combination of structural factors, including differences in local prescribing practices, thresholds for pharmacological vs. non-pharmacological treatment [19], and access to specialist psychiatric services, as well as possible sociocultural influences on help-seeking behavior. Nonetheless, the relevance of sociocultural and historic factors on these trends remains speculative in the absence of direct measurement of selected variables of interest. These factors encompass potential different cultural stances, which could result in a higher propensity to encourage combination treatment with ADs and/or psychosocial interventions [20].

In the current study, seven clusters of use were identified, reflecting distinct patterns of AD use that may map onto recognizable clinical trajectories. Cluster 1, characterized by the absence of any dispensing beyond the index prescription, probably represents a heterogeneous group encompassing patients who discontinued early due to adverse effects or personal preference or individuals for whom alternative pharmacotherapy was pursued. The disproportionate representation of tricyclic ADs in this cluster is consistent with both their less favorable tolerability profile relative to newer agents and their established use at subtherapeutic doses for nonpsychiatric conditions such as migraine, neuropathic pain, or insomnia, contexts in which the intended

duration of treatment may be inherently limited or contextual to active disease flare-ups [21–23]. Clusters 2 and 3, characterized by intermittent dispensing, may reflect episodic or recurrent psychiatric illness with re-engagement during symptomatic relapse, the adjunctive use of pharmacotherapy alongside primarily non-pharmacological management, or intermittent use for active disease flare-ups similarly to what described for Cluster 1 [23]. In contrast, Clusters 4–7 are more consistent with sustained, guideline-concordant maintenance therapy, as recommended by NICE for conditions such as recurrent major depressive disorder or generalized anxiety disorder [24, 25]. The greater ratio of SSRI users within these long-term clusters accords with previous evidence on the topic, albeit described for more limited samples or durations of treatment [26].

In a study conducted on the Swiss population, Amrein et al. [27] and colleagues described up to 57.4% of users with persistent AD use beyond 2 years. While our results show roughly half of this described cumulative prevalence (~27%, Clusters 5–7), older age and being a woman were also observed as factors associated with longer persistence in this neighboring region [27], indicating a potential for a generalizability of current findings beyond Italy alone.

Current results have direct implications for health policy, clinical practice, and research. Firstly, they warrant caution in the direct adoption of national pharmacoutilization results as shaping regional public health policies, considering how country-level results could not be able to address inter-regional heterogeneity correctly. Secondly, the current study also offers preliminary data for the possible adoption of difference–in–differences approaches at a later stage in pharmacoeconomic studies, possibly better establishing causality and magnitude of effects when considering health policies [28]. Finally, current results offer insight for healthcare providers. In fact, current guidelines promoting early treatment and diagnosis may require parallel efforts in developing evidence-based suggestions for treatment discontinuation.

While the current study represents a preliminary evaluation of regional trends, novel insight may ensue over future trends of regional pharmacoutilization, in case the two regions were to adopt diverging practices for what concerns healthcare management. Pharmacoepidemiology studies may leverage current results in light of synthetic control or difference–in–differences approaches. These methods could help better characterizing regional or national trends, considering that prescription patterns may be observed as diverging according to local practice, as evidence in the last decades not only in Europe [29, 30], but across the globe [31, 32].

Moreover, the present study represents a first and novel attempt to overcome the issue of non-integration in the digital data space between European regions. In fact, the current work represents a proof-of-concept for health data integration as an integral part of the future practice of pharmacovigilance in Europe. Specifically, the European Health Data Space framework offers at least three concrete pathways through which the present methodology could be extended: (1) cross-national pharmacovigilance, enabling near-real-time signal detection for unexpected patterns of long-term AD use or discontinuation across member states; (2) inter-regional and international benchmarking, allowing standardized comparison of utilization trajectories against established reference populations to identify outlier prescribing practices; and (3) evidence-based policy evaluation, supporting the prospective assessment of guideline implementation or reimbursement policy changes on AD prescribing patterns. Future studies will nonetheless face the challenge of translating real-world data into actionable policy recommendations while operating within the constraints of privacy legislation. Methodologies should ensure that only aggregate or sufficiently anonymized data are shared across jurisdictions. Approaches analogous to those here described can address this tension by embedding privacy-by-design principles without sacrificing the evidential rigor needed to draw policy-relevant conclusions.

4.1 | Limitations

The current study was carried out in a large population and had a long follow-up. Nonetheless, a more detailed characterization of the patients for each latent class of drug usage could aid in better describing long-term utilization patterns. An important limitation concerns the potential for off-label prescribing within the N06A* category. ADs, including tricyclic ADs, may have been issued for non-psychiatric indications, including neuropathic pain, insomnia, migraine prophylaxis, or fibromyalgia. This may partially explain the shorter time to discontinuation observed for other ADs in comparison to SSRIs. Future studies might then be interested in characterizing patterns of utilization for ADs in relation to, for instance, the specific diagnosis for which the prescription was issued, as well as better exploring the role of other socio-economic determinants of health. Individual-level socioeconomic variables (e.g., income, educational attainment, employment status) are not systematically recorded in the Italian administrative health databases used in this study and could not be included as covariates. Future studies incorporating indices of socioeconomic status could help disentangle social, economic, and other structural determinants of regional variation. Similarly, the administrative databases do not include clinical variables (e.g., pregnancy status, menopausal stage) necessary to conduct formal life-stage subgroup analyses in women, which would be a valuable direction for future research. Future studies might also investigate the influence of non-response rates to ADs, or the role played by transient or long-lasting side effects, as well as the ease of access to healthcare. In fact, a particular role in pharmacoutilization and retention may be played by specific prescription centers, at least when comparing primary and tertiary care centers [11]. Regarding incident user definition, a 5-year washout period was employed to minimize prevalent user contamination. However, AD use prior to the washout period or dispensed in other regions could not be captured, potentially leading to a slight overestimation of true incidence. Finally, the study was conducted before the COVID-19 pandemic, which substantially increased the incidence of depression and anxiety globally and may have altered prescribing patterns [33, 34]. Nonetheless, recent studies conducted on AD use in Italy show consistent temporal trends from 2017 onwards, limiting the potential bias of observations before the COVID-19 pandemic [35]. However, the pre-pandemic data analyzed may still provide a valuable baseline characterization of naturalistic AD utilization for future studies with the objective of quantifying COVID-19's impact on AD trends of use in more recent years.

5 | Conclusions

The long-term pharmacoutilization of ADs was shown as under the influence of structural and sociodemographic factors,

informing the observed heterogeneity in prevalence between neighboring regions in Italy. The present study establishes preliminary evidence for sociocultural factors driving prescription and utilization between neighboring regions within the same country. Implications for public health policies and future research are discussed, considering the recent directive by the European Commission on the European Health Data Space.

Author Contributions

Livio Tarchi: conceptualization, investigation, writing – original draft, writing – reviewing and editing. **Olga Paoletti**: conceptualization, data curation, investigation, methodology, formal analysis, writing – original draft. **Claudia Bartolini**: data curation, investigation, methodology, formal analysis, writing – review and editing. **Giuseppe Roberto**: data curation, investigation, methodology, formal analysis, writing – review and editing. **Rossella Miglio**: conceptualization, investigation, supervision, writing – review and editing. **Elisabetta Poluzzi**: conceptualization, investigation, supervision, writing – review and editing. **Ippazio Cosimo Antonazzo**: conceptualization, data curation, investigation, methodology, formal analysis, writing – review and editing. **Marco Menchetti**: conceptualization, investigation, supervision, writing – review and editing. **Carlotta Lunghi**: conceptualization, investigation, methodology, supervision, writing – review and editing. **Elisa Sangiorgi**: conceptualization, investigation, supervision, writing – review and editing. **Valdo Ricca**: conceptualization, investigation, supervision, writing – review and editing. **Giovanni Castellini**: conceptualization, investigation, supervision, writing – original draft, writing – review and editing. **Rosa Gini**: conceptualization, data curation, investigation, methodology, formal analysis, supervision, writing – original draft, writing – review and editing.

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Disclosure

The code used for data cleaning, analysis, and visualization can be obtained following reasonable request to the corresponding author.

Ethics Statement

The study was conducted as part of the activity plan of the Tuscan Regional Healthcare Agency (ARS Toscana), which is approved by its board and participated by the Regional Council of Tuscany, Italy.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. (*Supporting Information*)

Table S1: Shows characteristics at baseline for incident users. Table S2: Shows predictors of antidepressant prescription, according to a Poisson regression model. Table S3: Shows predictors of being assigned to clusters of use, according to logistic regression. Figure S1: Offers a graphical summary for patterns of antidepressant use within each cluster. Figure S2: Graphically illustrates patterns of antidepressant use, by time-point, within each cluster. Figure S3: Graphically illustrates sociodemographic characteristics of study participants within each catchment area by assigned cluster.