

Prevalence and Determinants of Long-Term Utilization of Antidepressant Drugs: A Retrospective Cohort Study

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Purpose: Antidepressant consumption has risen in recent years, driven by longer treatment duration. The objective of this study was to measure the prevalence of antidepressant long-term and chronic use in the Bologna area, Italy, and to identify their main determinants.

Materials and Methods: We conducted a retrospective claims-based cohort study by using the Bologna Local Health Authority data. A cohort of 18,307 incident users of antidepressant drugs in 2013 was selected, and subjects were followed for three years. A long-term utilization was defined as having at least one prescription claimed during each year of follow-up, while chronic utilization was defined as claiming at least 180 defined daily doses per year. Factors associated with chronic and long-term use were identified by univariate and multivariate logistic regressions.

Results: In our cohort, 5448 (29.8%) and 1817 (9.9%) subjects were dispensed antidepressants for a long-term course and in a chronically way, respectively. Older age, antidepressant polytherapy, polypharmacy, and being prescribed the first antidepressant by a hospital physician were all factors independently associated with chronic and long-term prescriptions of antidepressant drugs. Results were reported separately for men and women.

Conclusion: Antidepressant long-term and chronic prescriptions are common in the Bologna area. Because longer treatment should be clinically motivated, these results strongly prompt the need to evaluate the actual relevance, as they may indicate potentially inappropriate prescription patterns.

Keywords: antidepressants, depression, anxiety, anxiety disorders, primary care, pharmacotherapy, adherence, epidemiology, pharmacoepidemiology, treatment

Introduction

Antidepressant drugs are widely used, especially in developed countries, and their use has increased over the last few decades.¹⁻⁸ The higher number of prescriptions is associated with the increasing number of subjects being treated with these medications in primary care, along with the increased duration of treatment.^{7,9} Despite the fact that antidepressant drugs are being prescribed for different conditions, including neurological and rheumatoid diseases, as well as some off-label uses,^{10,11} the major indications are depressive and anxiety disorders,³ which often co-occur in the same subject,¹² accounting for about 75% of all prescriptions.^{3,5,13} Recent studies show, however, that the incidence of new prescriptions has not increased in the last few years, with the rise in prevalence of antidepressant use mainly due to an increased duration of treatment.^{7,9,14,15}

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Pharmacological treatment of depression^{3,5} is aimed at reducing depressive symptoms and preventing relapse.¹⁶ According to the National Institute for Health and Care Excellence (NICE) guidelines, antidepressant drugs should be continued for 6 months after remission of symptoms and should be maintained for a maximum of 2 years.^{16,17} Maintenance treatments longer than 2 years should be clinically motivated, such as for individuals with recurrent depression, or those with residual mood symptoms, or having a treatment-resistant depression.¹⁶

Similar treatment patterns should be used for anxiety disorders,^{18,19} with a delay of 2 to 8 weeks for symptom relief, and up to 12 weeks for a complete response. Similar to depression, long-term therapy should be applied for continuous improvement of symptoms and a reduced likelihood of relapse, with an optimal treatment duration of 12 to 24 months, even without studies on the efficacy and safety of antidepressant treatment with a follow-up of more than 12 months.^{18,19}

Antidepressant drugs are associated with many adverse effects, and their discontinuation may engender withdrawal symptoms.^{20,21} According to a recent systematic review, withdrawal symptoms largely vary in incidence rates (from 27% to 86%, with a weighted mean of 56%), duration and severity of symptoms.²¹ Notwithstanding this variation, which may depend on population studied, type of antidepressant used and duration of treatment, withdrawal symptoms seem very common and may increase the duration of antidepressant use without a clinical exigency. There is a lack of evidence on their efficacy and safety for long-term use²² since the majority of clinical trials conducted had follow-ups up to 8 months.^{23–25} Nevertheless, there is evidence that they are continued for long periods.^{15,26,27} Moreover, the use of antidepressants is associated with clinically important adverse events in susceptible populations, including weight gain, falls, and relevant cardiovascular events.^{28,29}

To the best of our knowledge, very few studies specifically analyze individual antidepressant drug use with follow-ups longer than two years, as well as factors associated with long-term or chronic use.^{15,30} This study was conducted due to the paucity of studies on long-term antidepressant prescription patterns. Also, it is important to identify long-term user characteristics to develop greater knowledge on this topic and highlight whether further study is warranted to verify a possible misuse of these drugs.

The objectives of this study were: 1. to estimate the prevalence of long-term antidepressant use, namely longer than two years; 2. to estimate the prevalence of chronic use, namely 180 daily defined doses (DDDs) of antidepressant medications per year for three years; 3. to examine the factors associated with long-term and chronic use in a cohort of subjects newly prescribed an antidepressant treatment in 2013, in Bologna, Italy.

Materials and Methods

Source of Data and Study Population

We conducted a retrospective population-based cohort study using prescription claims from the Bologna Local Health Authority (BLHA) during the period 2012–2016. In Italy, medical services are administered by the publicly funded National Health System (NHS), covering all the citizens and residents in the national territory. The Italian universal public healthcare system offers, thus, its population a universal public drug plan that allows all citizens to have equitable access to prescribed medications. Throughout the Italian territory, the NHS is organized at a regional level into Regional Health Authorities (RHA), and a local level into multiple Local Health Authorities (LHAs), responsible for providing health services to their local residents. RHA databases gather information collected by their LHAs for administrative purposes (reimbursing) on main health services (drug prescription, hospital admission, ambulatory visits, etc.). As for BLHA, all these databases cover a population of about 850,000 inhabitants living in the urban-rural area of Bologna, the main city of the Emilia-Romagna region in northern Italy. The BLHA administrative database contains information on insured subjects (unique identification number, gender, and age), on prescriptions claimed (drug names, trade names, claim date, number of packages dispensed and Anatomical Therapeutic Chemical Classification System [ATC] code), and on prescribers (identifier numbers and specialty), all linked through patient identification number. All essential drugs prescribed by general practitioners (GPs) and family pediatricians (FPs), such as antidepressants, are entirely (or partially, depending on income) reimbursed according to the Italian National Drug Formulary criteria, and almost all over-the-counter drugs, herbal medicines, and drugs used in hospitals or nursing homes are not included in these databases. Similarly, there is no information on the duration of the prescribed therapy, but the most common

prescription contains two packages of 30 tablets and covers a maximum of 60 days of therapy.

For the purpose of this study, we identified a cohort of subjects having claimed at least one antidepressant (ATC code N06A) in 2013, without any prescription the previous year, and who were continuously enrolled in the public drug plan of the BLHA from 2012 to 2016. Subjects who died during follow-up were excluded from the cohort because the assessment of treatment duration could not have been evaluated, otherwise. The date of the first prescription in 2013 was considered the index date. All subjects were followed for three years from their index date.

Definitions

Long-Term and Chronic Use of Antidepressant Drugs

Long-term use of antidepressants was defined as the presence of at least one claim recorded during each year of the three-year follow-up. Long-term use was further indicated as “chronic use”, if at least 180 DDDs³¹ of antidepressants were claimed during each year of the three-year follow-up.

Independent Variables

We collected the demographic characteristics of subjects present in the BLHA database (gender; age group; area of residence) and the information on prescriptions claimed: first antidepressant drug claimed [fifth level of the ATC system]; the presence of polytherapy (yes/no), defined as the presence of more than one antidepressant during follow-up; polypharmacy (yes/no), defined as the presence of claims for at least five different drugs^{32,33} (third level of the ATC system), other than antidepressants, during each year of follow-up; specialty of the first prescriber.

Statistical Analysis

Descriptive statistics were carried out to describe baseline characteristics of the study population. Differences between chronic and non-chronic use were evaluated with chi-square tests for categorical variables and Student's t-tests for continuous variables. Logistic regression analyses were used to identify factors associated with long-term and chronic use of antidepressants, testing for each variable, and calculating the unadjusted and adjusted odds ratios (OR and aOR, respectively) with a 95% confidence interval (CI) for all covariates. A variable was considered as statistically-significant for chronic or long-term use if it was associated with the outcome with a

p-value ≤ 0.05 . Interactions among independent variables were also analyzed and considered present if the p-value was ≤ 0.05 . All analyses were performed using RStudio and PostgreSQL statistical software.

Results

As shown in Figure 1, out of 870,507 inhabitants in the Bologna area in 2013 insured by the public drug plan of the BLHA, 18,307 were prescribed at least one antidepressant, without any prescriptions the previous year, with an incidence of 2.10%. Among them, 5488 subjects (29.9%) claimed at least one antidepressant during each year of the 3-year period and were therefore considered as having a long-term use for the purpose of this study. 1819 subjects (9.9% of the whole cohort) were dispensed at least 180 DDDs during each year of follow-up and were considered to have a chronic use of antidepressants.

Demographic and clinical characteristics of the entire cohort and of sub-cohorts having received chronic and non-chronic prescriptions are shown in Table 1. The

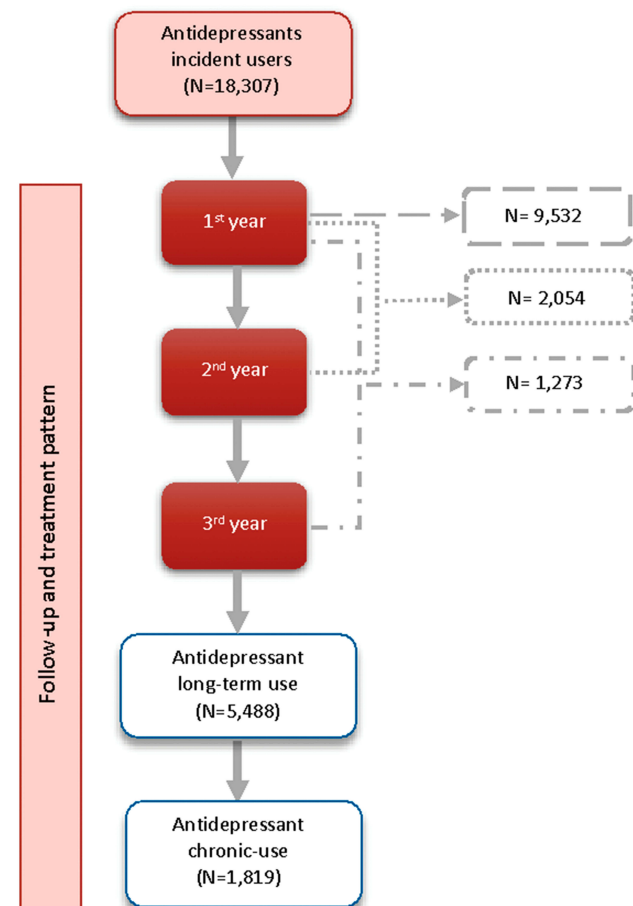


Figure 1 Synopsis of cohort selection and pattern distribution.

mean age of the study population was 58.46 years (18.24 SD) and 66.98% were women. Those being classified as having received long-term prescriptions claimed a mean of 257.1 DDDs in the first year of follow-up, 235.5 in the second year, and 232.2 in the third year. Among them, the most frequent antidepressants being dispensed were selective serotonin reuptake inhibitors (SSRIs), with sertraline as the most prescribed drug (26.2% of total drugs claimed), followed by paroxetine (16.1%), and citalopram

(13.9%). Trazodone was received by 11.3% of patients. Among those having received chronic treatment, the most prescribed antidepressants were sertraline (36.9%), paroxetine (15.0%) and citalopram (13.4%). Description of the first ten prescribed concomitant drug classes (at ATC II level) among chronic-prescribed and non-chronic-prescribed antidepressants during the follow-up are reported in Figure 2. There was little difference between those having chronic and non-chronic use: systemic

Table I Demographic Characteristics of Selected Cohort

Characteristics	Full Cohort N=18,307	Chronic Use N=1819	Non-Chronic Use N=16,488	P value
Gender				0.65
Male	6065 (33.13%)	594 (32.66%)	5471 (33.26%)	
Female	12,242 (66.87%)	1225 (67.34%)	11,017 (66.98%)	
Age [mean (SD)]	58.46 (18.24)	60.40 (17.52)	58.24 (18.30)	<0.001
Age class				<0.001
0–17	93 (0.51%)	10 (0.55%)	83 (0.50%)	
18–39	2979 (16.27%)	230 (12.64%)	2749 (16.71%)	
40–59	6432 (35.13%)	597 (32.82%)	5835 (35.48%)	
60–79	6096 (33.30%)	704 (38.70%)	5392 (32.78%)	
80+	2707 (14.79%)	278 (15.28%)	2429 (14.77%)	
Living area				<0.001
Urban	8159 (44.57%)	820 (45.08%)	7339 (44.62%)	
Rural	6669 (36.43%)	729 (40.08%)	5940 (36.11%)	
Missing	3479 (19.00%)	270 (14.84%)	13,279 (19.46%)	
First prescriber				0.85
GP	15,226 (83.17%)	1533 (84.28%)	13,693 (83.05%)	
Specialist	2743 (14.98%)	280 (15.39%)	2463 (14.94%)	
Missing	338 (1.85%)	6 (0.33%)	332 (0.201%)	
Initial antidepressant drug				<0.001
Sertraline	4798 (26.21%)	671 (36.89%)	4127 (25.09%)	
Paroxetine	2951 (16.21%)	273 (15.01%)	2678 (16.28%)	
Citalopram	2535 (13.85%)	244 (13.41%)	2291 (13.93%)	
Trazodone	2061 (11.26%)	60 (3.30%)	2001 (12.17%)	
Escitalopram	1512 (8.26%)	186 (10.23%)	1326 (8.06%)	
Amitriptyline	1390 (7.59%)	25 (1.37%)	1365 (8.30%)	
Venlafaxine	894 (4.88%)	105 (5.77%)	789 (4.80%)	
Duloxetine	675 (3.69%)	79 (4.39%)	596 (3.62%)	
Fluoxetine	496 (2.71%)	46 (2.53%)	450 (2.74%)	
Mirtazapine	336 (1.84%)	38 (2.09%)	298 (1.81%)	
Other	317 (1.73%)	18 (0.99%)	299 (1.82%)	
Polytherapy	342 (1.87%)	74 (4.07%)	268 (1.63%)	
Polypharmacy				<0.001
Yes	5411 (29.56%)	394 (21.66%)	5017 (30.50%)	
No	12,896 (70.44%)	1425 (78.34%)	11,471 (69.74%)	

Notes: Chronic use: at least 180 Defined Daily Dose (DDD) of antidepressant drug claimed in every year of follow-up. P values: all p-values but for age [mean (SD)], which was performed with independent Student *t* tests, were obtained by using chi square tests. Specialist: hospital or mental health center physician. Polytherapy: a combination of more than one antidepressant drugs as the initial treatment. Polypharmacy: 5 or more drugs claimed concomitantly.

Abbreviations: SD, standard deviation; GP, general practitioner.

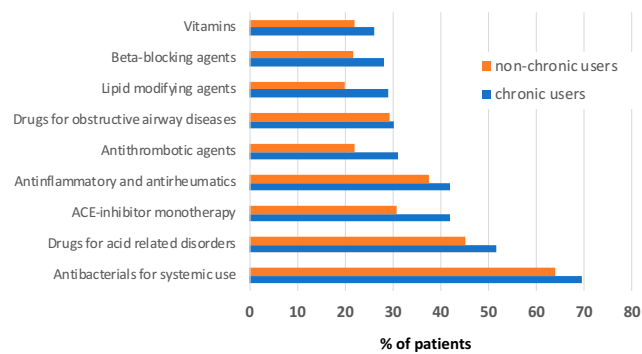


Figure 2 Description of the first 10 prescribed concomitant drugs classes (at ATC II level) among chronic and non-chronic users during the 3-year follow-up.

antibacterials (ATC: J01) and drugs against acid-related disorders (ATC: A02, mainly represented by proton pump inhibitors) were the first and second class in both groups of patients, followed by agents acting on the renin–angiotensin system (ATC: C09) and anti-inflammatory and antirheumatic agents (ATC: M01).

In the multivariate logistic regression analysis of chronic use (Table 2), gender and age, and age and living area resulted in having a significant interaction (p value < 0.05). We indeed performed the regressions separately for men and women. As reported in Table 2, risk factors determining a higher likelihood of chronic use were older age (especially in women and in rural settings), being prescribed the first antidepressant by a hospital or mental health center physician (especially in women, with an aOR of 3.45 and a 95% CI of 2.33–5.03), meeting criteria for polypharmacy. Compared to sertraline, the majority of antidepressant drugs were associated with a lower likelihood of chronic use (especially trazodone and amitriptyline), whereas receiving antidepressant polytherapy increased the likelihood of chronic use only among women.

Similarly, we performed separate regression analyses for men and women for long-term use since a statistically significant interaction was present between gender and polypharmacy and between initial drug and polypharmacy (p values < 0.005). Factors associated with overall long-term use are reported in Table 3. Older age was associated with a higher likelihood of long-term use among both genders, but among women, also those under 18 years old were at higher risk for long-term use, with an OR of 2.45 (compared to the class 18–39 years). Receiving the first prescription by a specialist showed similar ORs than those for chronic use. Amitriptyline was the only antidepressant associated with a lower risk of long-term use

among men without polypharmacy. Among both men and women with polypharmacy, also paroxetine, citalopram and trazodone showed lower risks. Among women without polypharmacy, citalopram and duloxetine resulted in a higher likelihood of long-term use, if compared to sertraline.

Discussion

Prevalence of Antidepressant Drug Utilization

This study provided new insights on chronic and long-term use of antidepressants and their determinants. The main finding of this study was that among patients having started an antidepressant treatment in 2013, about 30% were still being treated after more than two years, and about 10% of them claimed at least 180 DDDs each year for the three-year follow-up. Despite the extensive literature on antidepressant drug utilization,^{1–8,34,35} only one study, conducted in the United States, analyzed trends of antidepressant use with a follow-up period longer than two years at the patient level, ie, from 1999–2010.¹⁵ In that study, the authors found that the proportion of long-term use was extremely higher compared to our study, ranging from 46% in 1999–2000 to 67% in 2009–2010. Mojtabei et al used a self-reported measure of antidepressant duration, rather than an objective measure through pharmacy records; this may have overestimated the duration of treatment in that population.¹⁵ Moreover, the study was cross-sectional, with participants having longer treatment durations more likely to be selected for the study. These high proportions could be explained by the method for assessment of antidepressant use and the study design.

A more recent study in the Netherlands analyzed long-term antidepressant use (at least 15 months) from 1995 to 2015.³⁰ They found a trend similar to that reported by Mojtabei et al, but with lower proportions.^{15,30} In that study, more than 40% of their population claimed antidepressants for longer than 15 months (calculated from the first to the last prescription).³⁰ Despite the lower proportion than that reported by Mojtabei et al, the prevalence of long-term use was considerably higher than found in our study.³⁰ This can be partly explained by their definition of long-term use of 15 months, compared to our definition of treatment longer than two years. Moreover, they allowed interruptions between two consecutive prescriptions, while we imposed for our definition that the patient claimed at least one prescription of an antidepressant during each

Table 2 Logistic Regression Analysis of Factor Associated with Chronic Use of Antidepressant Drugs Among Men and Women Separately

Men						
Characteristics	Univariate Regression			Multivariate Regression		
	OR	95% CI	P value	OR	95% CI	P value
Age – Urban Area						
0–17	2.16	0.48–7.08	0.25	2.02	0.44–6.84	0.30
18–39	1	-	-	1	-	-
40–59	0.84	0.58–1.22	0.34	0.76	0.52–1.11	0.15
60–79	1.13	0.79–1.63	0.51	0.88	0.60–1.30	0.52
80+	0.82	0.49–1.34	0.44	0.69	0.40–1.16	0.17
Age – Rural Area						
0–17	3.74	0.80–13.07	0.05	4.60	0.95–17.26	0.03
18–39	1	-	-	1	-	-
40–59	1.21	0.78–1.93	0.41	1.11	0.71–1.79	0.65
60–79	1.77	1.15–2.80	0.01	1.43	0.92–2.30	0.12
80+	1.95	1.14–3.36	0.02	1.91	1.08–3.38	0.03
First Antidepressant Prescriber						
GP	1	-	-	1	-	-
Specialist	1.04	0.83–1.29	0.74	2.30	1.34–3.80	<0.01
Antidepressant Drug						
Sertraline	1	-	-	1	-	-
Paroxetine	0.62	0.48–0.79	<0.01	0.58	0.44–0.77	<0.01
Citalopram	0.55	0.42–0.72	<0.01	0.62	0.45–0.83	<0.01
Trazodone	0.15	0.09–0.23	<0.01	0.14	0.08–0.23	<0.01
Escitalopram	0.67	0.48–0.92	0.02	0.72	0.51–1.01	0.06
Amitriptyline	0.08	0.03–0.18	<0.01	0.09	0.03–0.19	<0.01
Venlafaxine	0.63	0.41–0.92	0.02	0.48	0.27–0.80	0.01
Duloxetine	0.49	0.29–0.78	<0.01	0.39	0.22–0.65	<0.01
Fluoxetine	0.58	0.30–1.03	0.08	0.66	0.32–1.20	0.20
Mirtazapine	0.84	0.48–1.39	0.53	0.84	0.41–1.56	0.61
Other	0.44	0.21–0.81	0.02	0.42	0.18–0.83	0.02
Polytherapy	1.47	0.89–2.34	0.11	1.34	0.66–2.55	0.39
Polypharmacy						
Non	1	-	-	1	-	-
Yes	1.63	1.34–1.98	<0.01	1.64	1.28–2.10	<0.01
Women						
Characteristics	Univariate Regression			Multivariate Regression		
	OR	95% CI	P value	OR	95% CI	P value
Age – Urban Area						
0–17	0.68	0.04–3.41	0.71	0.70	0.04–3.53	0.73
18–39	1	-	-	1	-	-
40–59	1.10	0.82–1.49	0.54	1.07	0.80–1.47	0.64
60–79	1.51	1.14–2.03	0.01	1.39	1.03–1.89	0.03
80+	1.55	1.13–2.16	0.01	1.56	1.11–2.20	0.01
Age – Rural Area						
0–17	1.45	0.23–5.13	0.63	1.74	0.27–6.36	0.47

(Continued)

Table 2 (Continued).

Men						
Characteristics	Univariate Regression			Multivariate Regression		
	OR	95% CI	P value	OR	95% CI	P value
18–39	1	-	-	1	-	-
40–59	1.71	1.22–2.45	<0.01	1.63	1.16–2.35	0.01
60–79	2.51	1.80–3.58	<0.01	2.26	1.60–3.24	<0.01
80+	3.00	2.07–4.41	<0.01	3.22	2.18–4.28	<0.01
First Antidepressant Prescriber						
GP	1	-	-	1	-	-
Specialist	1.00	0.85–1.18	0.97	3.45	2.33–5.03	<0.01
Antidepressant Drug						
Sertraline	1	-	-	1	-	-
Paroxetine	0.63	0.52–0.76	<0.01	0.73	0.60–0.89	<0.01
Citalopram	0.71	0.59–0.86	<0.01	0.77	0.62–0.94	0.01
Trazodone	0.21	0.15–0.28	<0.01	0.19	0.13–0.27	<0.01
Escitalopram	0.96	0.78–1.18	0.73	1.07	0.86–1.33	0.54
Amitriptyline	0.13	0.08–0.19	<0.01	0.14	0.08–0.22	<0.01
Venlafaxine	0.93	0.71–1.21	0.61	0.80	0.56–1.12	0.21
Duloxetine	1.02	0.76–1.35	0.89	1.14	0.84–1.54	0.39
Fluoxetine	0.65	0.44–0.93	0.02	0.69	0.45–1.03	0.08
Mirtazapine	0.73	0.45–1.14	0.19	0.84	0.46–1.41	0.53
Other	0.30	0.13–0.58	<0.01	0.19	0.06–0.46	<0.01
Polytherapy	1.82	1.30–2.51	<0.01	2.21	1.39–3.44	<0.01
Polypharmacy						
Non	1	-	-	1	-	-
Yes	1.56	1.35–1.81	<0.01	1.21	1.01–1.45	0.04

Notes: Specialist: hospital or mental health center physician; Polytherapy: a combination of more than one antidepressant drugs as the initial treatment. Polypharmacy: 5 or more drugs claimed concomitantly.

Abbreviations: OR, odds ratio; 95% CI, 95% Confidence Interval; GP, general practitioner.

year of the three-year follow-up (and 180 DDDs per year for chronic use).³⁰ Therefore, the proportion of long-term use was lower than reported in other studies in Europe and the United States,^{15,30} even if comparisons are not evident due to differences in the definitions of drug exposure and study designs.

It must be acknowledged that, despite the majority of subjects with depression who recover rapidly (within a few months), a minority of these patients experience a longer course of depressive symptoms.³⁶ In 2004, a systematic review analyzed the prevalence of recovery, recurrence, and chronicity of depression in general practice and the community.³⁶ The authors, examining the results of published prospective longitudinal studies, reported that the prevalence of chronic courses of depression ranged from 10 to 17%.³⁶ The prevalence of long-term users in our population could be explained by the proportion of

subjects experiencing chronic courses of depression or those at higher risk of recurrence. Recently, in a study on the duration of depressive episodes in the general Dutch population, the authors reported that about 74% of subjects in their cohort recovered from depression within one year, 84% within two years, and 88% within three years.³⁷ The authors estimated about 20% for the prevalence of chronic depression, which is in accordance with the proportion of long-term use in our study.

Moreover, antidepressants such as SSRIs and selective serotonin-norepinephrine reuptake inhibitors (SNRIs) are considered as first-line pharmacological treatment choices, not only for depression, but also for anxiety disorders.³⁸ Due to the frequent chronic course of anxiety disorders,³⁹ pharmacological treatment may be continued for long periods. We found frequent prescriptions of antidepressants that are second-line treatments for depression (ie,

Table 3 Logistic Regression Analysis of Factor Associated with Long Term Use of Antidepressants Among Men and Women Separately

Men						
Characteristics	Univariate Regression			Multivariate Regression		
	OR	95% CI	P value	OR	95% CI	P value
Age						
0–17	1.95	0.98–3.78	0.47	2.22	0.98–4.82	0.05
18–39	1	-	-	1	-	-
40–59	1.04	0.88–1.22	0.66	1.00	0.83–1.22	0.97
60–79	1.33	1.13–1.57	<0.01	1.31	1.07–1.61	0.01
80+	1.26	1.02–1.55	0.03	1.60	1.23–2.07	<0.01
Living Area						
Urban	1	-	-	1	-	-
Rural	0.92	0.82–1.05	0.21	0.92	0.81–1.05	0.22
First Antidepressant Prescriber						
GP	1	-	-	1	-	-
Specialist	1.06	0.91–1.22	0.47	2.69	1.77–4.11	<0.01
Antidepressant Drug – No Polypharmacy						
Sertraline	1	-	-	1	-	-
Paroxetine	1.05	0.77–1.44	0.74	1.33	0.93–1.92	0.12
Citalopram	0.99	0.71–1.36	0.94	1.03	0.69–1.53	0.88
Trazodone	0.60	0.37–0.95	0.03	0.59	0.31–1.08	0.10
Escitalopram	1.19	0.81–1.73	0.36	1.34	0.88–2.04	0.17
Amitriptyline	0.36	0.18–0.65	<0.01	0.38	0.18–0.74	0.01
Venlafaxine	0.89	0.57–1.38	0.62	1.13	0.63–1.96	0.67
Duloxetine	0.63	0.29–1.23	0.20	0.66	0.29–1.37	0.29
Fluoxetine	0.95	0.47–1.79	0.87	1.17	0.54–2.38	0.68
Mirtazapine	0.91	0.43–1.79	0.80	0.87	0.31–2.13	0.78
Other	1.49	0.80–2.69	0.19	1.25	0.57–2.56	0.56
Polytherapy	0.59	0.20–1.45	0.29	0.61	0.09–2.42	0.53
Antidepressant Drug - Polypharmacy						
Sertraline	1	-	-	1	-	-
Paroxetine	0.77	0.62–0.95	0.01	0.77	0.61–0.96	0.02
Citalopram	0.75	0.59–0.94	0.01	0.73	0.56–0.93	0.01
Trazodone	0.70	0.57–0.87	<0.01	0.77	0.60–0.97	0.03
Escitalopram	0.82	0.62–1.08	0.16	0.85	0.63–1.14	0.28
Amitriptyline	0.39	0.27–0.55	<0.01	0.43	0.30–0.61	<0.01
Venlafaxine	0.71	0.50–1.01	0.06	0.77	0.50–1.16	0.21
Duloxetine	0.46	0.31–0.66	<0.01	0.42	0.27–0.62	<0.01
Fluoxetine	0.68	0.40–1.13	0.15	0.75	0.42–1.28	0.30
Mirtazapine	1.23	0.78–1.92	0.37	1.38	0.78–2.41	0.26
Other	0.54	0.31–0.88	0.02	0.54	0.30–0.94	0.04
Polytherapy	1.85	1.18–2.92	0.01	1.56	0.83–2.94	0.16
Women						
Characteristics	Univariate Regression			Multivariate Regression		
	OR	95% CI	P value	OR	95% CI	P value
Age						
0–17	1.30	0.69–2.32	0.39	2.45	1.23–4.74	0.01

(Continued)

Table 3 (Continued).

Men						
Characteristics	Univariate Regression			Multivariate Regression		
	OR	95% CI	P value	OR	95% CI	P value
18–39	1	-	-	1	-	-
40–59	1.45	1.28–1.65	<0.01	1.30	1.12–1.49	<0.01
60–79	1.76	1.55–2.00	<0.01	1.64	1.42–1.90	<0.01
80+	1.89	1.64–2.19	<0.01	2.25	1.90–2.67	<0.01
Living Area						
Urban	1	-	-	1	-	-
Rural	0.94	0.87–1.03	0.19	0.96	0.88–1.05	0.36
First Antidepressant Prescriber						
GP	1	-	-	1	-	-
Specialist	0.79	0.71–0.89	<0.01	2.38	1.70–3.33	<0.01
Antidepressant Drug – No Polypharmacy						
Sertraline	1	-	-	1	-	-
Paroxetine	1.16	0.90–1.50	0.25	1.31	0.98–1.75	0.07
Citalopram	1.34	1.03–1.73	0.03	1.42	1.05–1.92	0.02
Trazodone	0.79	0.54–1.12	0.20	0.82	0.52–1.27	0.38
Escitalopram	1.60	1.19–2.15	<0.01	1.66	1.20–2.30	<0.01
Amitriptyline	0.40	0.25–0.62	<0.01	0.40	0.23–0.66	<0.01
Venlafaxine	1.40	0.92–1.99	0.06	0.96	0.57–1.58	0.89
Duloxetine	1.80	1.10–2.88	0.02	2.14	1.26–3.59	<0.01
Fluoxetine	0.59	0.33–0.98	0.05	0.50	0.26–0.90	0.03
Mirtazapine	1.01	0.55–1.76	0.98	1.17	0.50–2.48	0.70
Other	0.95	0.49–1.75	0.88	0.65	0.26–1.43	0.32
Polytherapy	1.53	0.86–2.62	0.13	2.27	0.75–6.45	0.13
Antidepressant Drug - Polypharmacy						
Sertraline	1	-	-	1	-	-
Paroxetine	0.78	0.68–0.90	<0.01	0.84	0.72–0.98	0.02
Citalopram	0.80	0.69–0.92	<0.01	0.81	0.69–0.95	0.01
Trazodone	0.80	0.69–0.94	0.01	0.81	0.68–0.96	0.01
Escitalopram	1.09	0.92–1.29	0.34	1.15	0.96–1.37	0.13
Amitriptyline	0.45	0.37–0.55	<0.01	0.48	0.39–0.58	<0.01
Venlafaxine	0.86	0.68–1.08	0.20	0.77	0.58–1.01	0.06
Duloxetine	0.90	0.71–1.14	0.38	0.98	0.76–1.26	0.88
Fluoxetine	0.81	0.61–1.07	0.14	0.83	0.61–1.13	0.24
Mirtazapine	0.76	0.52–1.11	0.17	0.70	0.44–1.07	0.11
Other	0.88	0.59–1.30	0.53	0.80	0.51–1.23	0.32
Polytherapy	1.45	1.05–1.99	0.02	1.64	1.07–2.54	0.02

Notes: Specialist: hospital or mental health center physician; Polytherapy: a combination of more than one antidepressant drugs as the initial treatment. Polypharmacy: 5 or more drugs claimed concomitantly.

Abbreviations: OR, odds ratio; 95% CI, 95% Confidence Interval; GP, general practitioner.

trazodone and paroxetine). A higher sedative effect of these drugs may suggest a possible use for treating anxiety symptoms. Trazodone is also used off-label for insomnia in elderly, and paroxetine can be the first-choice SSRI in patients receiving polypharmacy or with liver failure since it is the only SSRI excreted without CYP metabolism.

Another possible explanation is that trazodone and paroxetine can also be taken at low doses since trazodone is available in drops and paroxetine in scored tablets. A recent meta-analysis on the risk of relapse of anxiety disorders after antidepressant discontinuation found that patients on treatment for at least one year had a lower

relapse rate compared to subjects who were discontinued earlier.⁴⁰ Unfortunately, there is a lack of evidence for longer duration of treatment for anxiety disorders in terms of efficacy, safety (withdrawal effect), and patient preferences.^{22–25} Yet, given the chronicity of anxiety disorders, a certain proportion of long-term antidepressant treatments may be expected. Besides, patients suffering from anxiety symptoms could be more afraid of stopping antidepressants and having negative experiences with drawbacks.⁴¹ Qualitative studies have investigated the reasons behind the difficulties of withdrawing antidepressants.^{42,43} They found that patients are generally more afraid of discontinuing medications than persist taking them. They also consider that their wellbeing is linked to the continued use of antidepressants because of the chronicity of their conditions.^{42,43}

Although long-term treatment with antidepressants should be suitable for individuals with chronic depression, those with a high risk of relapse, or patients with anxiety disorders as defined by clinical guidelines, there are no sufficient evidence-based studies for the appropriate duration of antidepressant treatment for these subgroups of patients.^{16,44}

As for the percentage of patients with long-term but not chronic use (about 20%), it should be recognized that they probably received recurrent very short courses of antidepressants, which, per se, suggest stronger inappropriateness in comparison with chronic use. Six-month cycles seem not reached at all indeed, and recurrence of disease episodes could be the reason for subsequent cycles.

Determinants of Long-Term and Chronic Use

This study also identified some demographic and clinical factors associated with chronic and long-term use. We found that older age and polypharmacy were associated with a higher risk for a longer duration of antidepressant treatment, both in the univariate and multivariate analyses, with higher odd ratios for the age group of 80-years-old and above. This finding is in line with what has been reported in other studies on long-term treatment,^{15,30} which could be due to the higher level of chronicity of depression in the elderly,⁴⁵ or the fact that older patients may take more time to show a response and are less likely to discontinue their treatment.¹⁸ Older subjects are also more likely to be affected by multiple chronic conditions (multimorbidity) and to take many medications (polypharmacy).⁴⁶ Regardless of age, a higher

number of drugs has been associated with a higher probability of depression,⁴⁷ while a recent systematic review found that depression was more frequent in subjects with multimorbidity.⁴⁸ Some medications may cause depression as an adverse effect, so a recent study found that patients taking antidepressants along with potential depression-inducing medications, such as hormonal contraceptives, β -blockers, corticosteroids, or anti-obesity drugs were more likely to report depressive symptoms than patients taking only antidepressant drugs.^{49–51} Women are more likely to suffer from anxiety and depressive disorders. In our analyses, gender interacted with age (for chronic use) and initial drug (for long-term use), so the analyses were reported separately for men and women. Other studies found no association between gender and chronic or long-term use.^{15,30}

Being prescribed the first antidepressant by hospital physicians or those specializing in mental health was associated with a higher risk of chronic and long-term use, with significant aORs of 2.30–3.45, depending on gender. The higher risk for more prolonged antidepressant use among those prescribed by a specialist could be justified by the fact that more severe cases of depression, which are possibly those with a high risk of relapse or with treatment-resistant depression, are likely referred directly to mental health specialists by general practitioners.⁵² Other studies on antidepressants⁵³ or other drugs^{54,55} have used the specialty of the prescriber as a proxy for disease severity or complexity. Another possible explanation of these results is that patients receiving a prescription by a specialist rather than a GP may be more likely to feel that its treatment was helpful,⁵⁶ and they might be more persistent.^{13,57} A study by Pomerantz et al,¹³ based on administrative data of a health maintenance organization in the United States linked to a physicians' survey, showed that specialist practitioners (ie, psychiatrists) prescribed more prolonged courses of antidepressant treatment, with their patients being more prone to follow their recommendations. Although some studies reported a higher prevalence of diagnosed depression in urban vs rural living areas,^{47,58} we did not find any association between the area and duration of antidepressant treatment. This finding may indicate that in our population, patients have equitable access to mental health resources, irrespective of residence, access that is assured by the diffused presence of family physicians and LHAs of the Italian health-care system integrated with a specific collaboration program started in 1999.⁵⁹

Among antidepressants as initial treatment, we found that only sertraline was associated with a higher risk for chronic use. Men and women with polypharmacy (and,

therefore, probably multimorbid) showed similar associations between first drug and long-term use. SSRIs, which are generally used for their favorable pharmacological profile in the general population, can cause significant side effects due to drug-drug interactions.^{60,61} Among SSRIs, sertraline is usually preferred, especially in the elderly, due to its favorable risk-benefit profile, because of its lower likelihood of interaction with other drugs in multimorbid patients.¹⁷ Sertraline could, therefore, be preferred in more complicated clinical cases (eg older or multimorbid patients). Among patients not exposed to polypharmacy, only amitriptyline showed a lower risk for long-term use, and citalopram and duloxetine showed a higher risk only among women. Amitriptyline is also used for short periods, at low dosages, for insomnia or headache, and duloxetine can be used for long periods for chronic pain related to fibromyalgia, diabetic neuropathy or other painful syndromes.^{62,63} Patients who use duloxetine may be afraid to come back to pain if they stop treatment. These results are nevertheless more complicated to interpret, and further studies are needed to investigate the reasons for prescribers' clinical choices regarding different antidepressants.

Strengths and Limitations

The main strength of this study is its large population that represents virtually all residents of the Bologna area having started a treatment course with an antidepressant drug in 2013. The Italian health system is fully public and covers all the resident population. Another strength is that we identified subjects newly treated with antidepressants since they did not have any prescription in the previous year. Moreover, we followed all the patients for a period of three years, starting from the first prescription claimed, recording all the prescriptions claimed in this period. Furthermore, the BLHA databases are of high quality, as they are meant for reimbursement purposes, and they are largely used for research and surveillance purposes.^{1,64-66}

This study, however, has some limitations. First, the BLHA database does not have information on diagnosis, clinical evaluations, or indications for prescriptions. We were thus unable to characterize subjects according to a diagnosis of depressive or anxiety disorder and did not know the reason for the prescriptions received. The indications could have been other than depression or anxiety, such as other psychiatric or non-psychiatric diseases, which could need longer durations of treatment. However, no other possible indication of use could justify an evidence-based long-term or chronic use, so far.

Moreover, the large majority of patients use antidepressants for these two disorders, which share similar guidelines for pharmacotherapy in terms of antidepressant classes used and duration of treatment.^{3,5,13} Information on ethnicity or income could have been valuable as potential factors associated with the chronicity of antidepressant use, but this information is not in our databases. However, in the previously cited Dutch study, socioeconomic status was not associated with long-term use of antidepressants.³⁰ Moreover, antidepressant drugs are covered by the Italian public drug plan, and the proportion of patients purchasing them privately is negligible.⁶⁷ Finally, certain drugs, such as trazodone, amitriptyline and mirtazapine, may be prescribed at daily doses lower than 1 DDD. Unfortunately, we cannot quantify this information bias, which is inherent to the use of the ATC-DDD system (which is, in turn, necessary since there no information about day's supply in the BLHA databases). Nevertheless, this misclassification could have only underestimated actual chronic use.

Conclusion

Long-term and chronic use of antidepressants is common in the Bologna area, and this phenomenon may contribute to the increased prevalence and exposure level of antidepressants at a population level. Because of the administrative data we used, it is not possible to know if a long duration was clinically motivated, nor the proportion of unnecessary long-term use. Clinical guidelines indicate that durations of about 12–24 months should be targeted, with more prolonged treatments clinically motivated, mainly because of the lack of evidence on the risk/benefit ratio of long-term use. Reasons for a longer duration should be investigated to highlight the possible presence of potentially inappropriate prescription patterns. Risk factors for long-term and chronic use (older age, presence of other comorbidities, prescriptions made by a specialist, or the type of antidepressant prescribed) may suggest acceptable reasons for prolonged use. Specific antidepressants (ie, duloxetine) may be used for chronic pain, especially by women, presumably for longer periods than for depression. Similar considerations can be addressed for people with an anxiety disorder, for whom the clinician may find it more difficult to deprescribe antidepressants for fear of anxiety symptoms reappear. Specific subpopulations identified as being at higher risk for a long term and chronic use with this study should, therefore, be addressed for further research studies, and indications for antidepressant use should be investigated deeply.

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Ethics

Ethics approval was obtained from the Ethical Committee of the Local Health Authority “Area Vasta Emilia Centro” (CE 18137).

Disclosure

The authors declare that they have no conflicts of interest regarding this article.

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