Increased antidepressant use during the COVID-19 pandemic: Findings from the Friuli Venezia Giulia region, Italy, 2015–2020

Laura Pazzagli [a], Johan Reutfors [a], Ejlli Lucian [b], Giovanna Zerial [b], Alfredo Perulli [b], Giulio Castelpietra [*,b]

[a] Centre for Pharmacoepidemiology, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden
[b] Central Health Directorate, Friuli Venezia Giulia region, Riva Nazario Sauro 8, Trieste 34100, Italy

A B S T R A C T

Background: Few studies investigated the impact of the pandemic on antidepressant (AD) use.
Methods: The Social and Health Information System of Friuli Venezia Giulia region, Italy, provided data on AD use. Sex, age, AD class and month used the amount of AD prescriptions, measured by defined daily doses (DDD) per 1000 inhabitants per day, to compare AD use in 2020 with the period 2015–2019. A linear trend model predicted AD use for 2020, based on years 2015–2019.
Results: AD use was on average 20% higher in each month of 2020 when compared with the same month for the period 2015–2019, with an increase of more than 30% in the first four and in the last two months of 2020. The observed AD use in 2020 was higher than predicted, particularly in men, and in the 30–59 years age group.
Limitations: Descriptive study of AD use without analysis of data at the individual level. No information on psychiatric diagnoses of AD users.
Conclusion: AD use was higher in the first year of the COVID-19 pandemic. Further research is warranted to understand if this may be related to a rise in mental disorders in the general population during the COVID-19 pandemic.

1. Introduction

The SARS-CoV-2 (COVID-19) pandemic has caused an increased burden on public health and social systems worldwide, and a deterioration of mental health has been claimed in several populations (Carr et al., 2021; Ettman et al., 2020; Pierce et al., 2020; Winkler et al., 2021). In particular, studies from Europe and the United States have found a rise in affective and anxiety disorders compared with the pre-COVID-19 period (Ettman et al., 2020; Jacob et al., 2020; Winkler et al., 2021). To date, however, few researchers have investigated the impact of the pandemic on antidepressant (AD) use, and the results are somewhat conflicting. A study based on the British National Health Service (NHS) database on AD prescriptions, observed an increase in ADs during the COVID-19 pandemic compared to the previous period (Rabeea et al., 2021). Similarly, a report from Portugal showed an increase in AD use from March 2020 (Estrela et al., 2021). In contrast, studies from all United Kingdom (UK) general practice, Germany and Portugal found a slight decrease (Carr et al., 2021; Jacob et al., 2020).

Italy was the first European country to face the pandemic emergency. The Italian Government imposed a national lockdown from the 9th of March to the 17th of May, 2020, introducing several restrictions, including the temporary closure of non-essential services, productive activities and businesses. At that time Italy was the European country with the highest incidence of COVID-19 cases. Afterwards, the restrictions were reduced during the summer of 2020. A new lockdown period was then imposed by the Government from mid-October 2020 until the end of the year, with a modulation of restrictions at regional level following the burden of the pandemic on the health care system and the incidence of cases. Given this context, researchers have identified an increase of depression and anxiety disorders, as well as sleeping disturbances, in Italy during the first lockdown (Castellini et al., 2021; Cellini et al., 2020; Gualano et al., 2020; Mazza et al., 2020; Rossi et al., 2020), but little is known on AD use in this period. A report by the Italian Medicines Utilisation Monitoring Centre found no significant trend in the number of packages of ADs used per 10,000 inhabitants per day when comparing the first two months of 2020 to March and April

(Agenzia Italiana del Farmaco, 2020). A recent Italian study from Tuscany found a reduction in AD use in the first-lockdown, with a rebound in the post first-lockdown, which reached higher level than predicted by the pre-lockdown AD prescriptions' trend (Antonazzo et al., 2022). However, no stratified analyses based on sex and age of AD users, neither on AD class, were provided.

Friuli Venezia Giulia (FVG) is an autonomous region in the north-east of Italy with a population of 1.2 million inhabitants. Healthcare information in FVG are provided by the Regional Social and Health Information System (SISSR), which involves different registers (Castelpietra et al., 2008, 2017, 2019).

The aim of the present study is to describe the number of defined daily doses (DDDs) per 1000 inhabitants per day of ADs dispensed in FVG during year 2020 compared with the period 2015–2019 by sex, age, AD class and month. Additionally, observed amount of use of ADs in DDDs is presented together with the predicted amount of use that would have been observed if AD use in 2020 would have followed the patterns observed in the five years before the COVID-19 pandemic (2015–2019).

2. Material and methods

2.1. Data sources

We used the Drug Prescription Register, which covers all prescriptions dispensed in the Region FVG prescribed by general practitioners (GPs) or other physicians working for the public health care system. This register covers more than 90% of filled prescriptions (Castelpietra et al., 2008), which are reimbursed by the Italian National Health System, All dispensed prescriptions of ADs included in the Drug Prescription register of FVG from 2015 to 2020 (6 years) were included in the study. The data included the date of prescriptions, the number of packages, the amount prescribed expressed in DDDs, the substance name according to its ATC code (WHO Collaborating Centre for Drug Statistics Methodology, 2015), together with the sex and age of the prescription's owner. Data were aggregated according to the date of prescriptions: this meant that the Register provided the total number of packages dispensed each day, according to sex, year of age and AD type.

2.2. Data management

We divided the ADs into four classes, according to ATC-code: tricyclics - TCA (ATC-code N06AA); Selective Serotonin Reuptake Inhibitors - SSRI (N06AB); Serotonergic Noradrenergic Reuptake Inhibitors - SNRI (venlafaxine (N06AX21), duloxetine (N06AX16)); other ADs (agomelatine (N06AX22), buproione (N06AX12), mirtazapine (N06AX11), vortioxetine (N06AX26), mianserine (N06AX03), reboxetine (N06AX18), trazodone (N06AX05)). In order to obtain the total amount of DDD dispensed per date in each category of interest (i.e. sex, age groups and AD classes), DDDs were multiplied for the number of packages.

2.3. Statistical analyses

Data on observed number of DDDs used from 2015 to 2019 and in 2020 were used to calculate the DDDs per 1000 inhabitants per day according to sex, age group (0–29 years, 30–59 years, >60 years), AD class and month. Additionally, data on observed number of DDDs used from 2015 to 2019 were used to predict AD use in 2020. A linear trend model was used to predict the number of DDDs use according to prescription date. The number of the month and week were also included in the model to account for seasonality. Finally, the monthly means of the predicted number of DDDs for 2020 were plotted together with the monthly means of the observed number of DDDs in 2020. The prediction analyses were repeated by sex, age, and AD class respectively.

3. Results

A total of 75,725,552 DDDs of AD were dispensed from 2015 to 2019 and used to predict the potential number of DDDs prescribed in 2020. The observed number of DDDs in 2020 was of 17,766,301. When stratifying the analyses by sex and age, due to missing values for the two variables, the number of DDDs dispensed was reduced to 75,123,946 from 2015 to 2019, and to 17,680,595 in 2020. The variable containing ATC codes did not contain missing values and the analyses stratified by AD class were conducted using all DDDs.

In the pre-COVID period (years 2015–2019), as well as in 2020, around 70% of DDDs of AD were dispensed to women and to individuals of age ≥60 years. About half of DDDs dispensed were SSRIs, followed by SNRIs, other ADs and TCAs (Table 1).

The number of DDDs per 1000 inhabitants per day increased overall by 20% in 2020 when compared to the period 2015-2019. This increase was reported in all the analyses stratified by sex, age, and AD class, with the exception of the TCA where the number remained constant in the two periods. The highest increases were observed in the young age group, particularly in men (Table 1).

The dispensed DDDs per 1000 inhabitants per day showed an increase during each month of the year 2020 with the highest increase in the first four months of 2020, particularly in March (from 2.7 to 3.8 DDDs per 1000 inhabitants per day), and in November and December (Table 2).

The prediction analyses showed that 2020 had higher monthly means for the observed number of DDDs compared to the monthly means of the number of DDDs predicted based on data from 2015 to 2019 (Fig. 1). Both sexes had higher monthly means for the observed number of DDDs compared to the predicted during all months, except for women in April and May (Fig. 2). In the analysis stratified by age, the age group 30–59 years had higher monthly means for the observed number of DDDs dispensed during all months of 2020. The same applied to the 60 years and more age group, with the exception of April and October, where the observed and predicted monthly means were equal. Inversely, the age group 0–29 years showed a mix pattern, with months in which the mean number of observed DDDs was higher than the predicted, and vice versa (Fig. 3). Finally, the analysis stratified by AD class showed that other ADs had higher monthly means for the observed number of DDDs dispensed during all months of 2020, followed by SSRI which showed observed monthly means similar to the predicted only in April and May, and SNRI, which showed higher monthly means for the observed number of DDDs than the predicted in the first four months of 2020. TCA showed an inverse trend, with the monthly means of the predicted number of DDDs higher than the observed in most of the months (Fig. 4).

4. Discussion

In this study based on data from a population of more than one million people of north eastern Italy, there was an average 20% increase in the amount of DDDs per 1000 inhabitants of ADs dispensed during the year of the COVID-19 pandemic 2020 compared to previous years, with the highest increase among young men. In particular, more than 30% increase of DDDs per 1000 inhabitants of AD was observed in the first four months of 2020, as well as in November and December. Moreover, the observed number of DDDs dispensed was higher than the predicted in men, in adults aged 30 to 59 years, and for SSRIs and other ADs classes.

An increasing trend in AD use has been observed in Italy and in other European countries in the pre-COVID period (Chen et al., 2022; Gomez-Lumbreras et al., 2019; Gualano et al., 2014), in line with our data including the first two months of 2020. However, previous data on AD use during the pandemic has shown mixed patterns. A British study observed an increase of ADs, in particular SSRIs, dispensed from January to September 2020 and compared to the three previous years, using a

Table 1
Defined daily doses (DDDs) dispensed per day in 2015-2019 and in year 2020, and relative variation of DDDs per 1000 inhabitants, according to sex, age groups and antidepressant (AD) classes.

Years Sex[a]	2015–2019 Total N of DDDs	%	N of DDD per 1000 inhabitants	2020 Total N of DDDs	%	N of DDD per 1000 inhabitants	Percentage change of DDDs (%)
Women	53,818,686	71.1	24.3	12,690,708	71.4	29.0	19
Men	21,305,260	28.1	9.6	4,989,887	28.1	11.4	19
Age group [a]							
0-29	1,848,688	2.4	0.8	508,775	2.9	1.2	50
30-59	24,537,417	32.4	11.1	5,367,618	30.2	12.3	11
≥ 60	48,737,841	64.4	22	11,804,202	66.4	27	23
Age group for women							
0-29	1,105,249	1.5	0.5	302,525	1.7	0.7	40
30-59	16,901,828	22.3	7.6	3,711,490	20.9	8.5	12
≥ 60	35,811,609	47.3	16.2	8,676,693	48.8	19.8	22
Age group for men [a]							
0-29	743,439	1.0	0.3	206,250	1.2	0.5	67
30-59	7,635,589	10.1	3.4	1,656,128	9.3	3.8	12
≥ 60	12,926,232	17.1	5.8	3,127,509	17.6	7.1	22
AD class							
TCA	8,611,275	11.4	3.9	1,684,705	9.5	3.9	0
SSRI	37,646,600	49.7	17.0	8,769,110	49.4	20.0	18
SNRI	19,362,040	25.6	8.7	4,658,990	26.2	10.6	22
Other ADs	10,105,637	13.4	4.6	2,653,496	14.9	6.1	33
AD class for women							
TCA	6,466,885	8.5	2.9	1,275,140	7.2	2.9	0
SSRI	26,770,240	35.4	12.1	6,234,390	35.1	14.2	17
SNRI	13,891,720	18.3	6.3	3,421,510	19.3	7.8	24
Other ADs	6,689,841	8.8	3.0	1,759,668	9.9	4.0	33
AD class for men							
TCA	2,062,650	2.7	0.9	402,865	2.3	0.9	0
SSRI	10,567,850	14	4.8	2,487,570	14	5.7	19
SNRI	5,337,570	7.1	2.4	1,220,430	6.9	2.8	17
Other ADs	3,337,190	4.4	1.5	879,022	5.0	2.0	33

N number; DDD Defined Daily Dose; TCA Tricyclics Antidepressant; SSRI Selective Serotonin Reuptake Inhibitor; SNRI Serotonergic Noradrenergic Reuptake Inhibitors; AD Antidepressant.

[a] 601,606 (0.8%) of DDDs had missing information.

Table 2
Defined daily doses (DDDs) of antidepressants (ADs) dispensed per day in years 2015–2019 and in year 2020, and relative variation of DDDs per 1000 inhabitants, according to month.

Years Month	2015–2019 Total N of DDDs	%	N of DDD per 1000 inhabitants	2020 Total N of DDDs	%	N of DDD per 1000 inhabitants	Percentage change of DDDs (%)
January	5,807,658	7.7	2.6	1,474,852	8.3	3.4	31
February	5,406,361	7.1	2.4	1,417,091	8.0	3.2	33
March	5,976,307	7.9	2.7	1,652,640	9.3	3.8	41
April	5,603,360	7.4	2.5	1,395,734	7.9	3.2	28
May	6,111,439	8.1	2.8	1,357,158	7.6	3.1	11
June	6,158,995	8.1	2.8	1,455,303	8.2	3.3	18
July	7,487,282	9.9	3.4	1,585,011	8.9	3.6	6
August	7,009,485	9.3	3.2	1,364,582	7.7	3.1	-3
September	7,188,015	9.5	3.2	1,488,423	8.4	3.4	6
October	7,296,258	9.6	3.3	1,555,373	8.8	3.6	9
November	5,867,882	7.8	2.6	1,471,781	8.3	3.4	31
December	5,812,510	7.7	2.6	1,548,353	8.7	3.5	35

N number; DDD Defined Daily Dose.

prescription cost analysis database run by the National Health Service Business Services Authority (Rabeea et al., 2021). A report from Portugal based on public physicians' prescriptions from January 2018 to July 2020, also showed an increase in ADs dispensed starting from March 2020 (Estrela et al., 2021). In contrast, from the UK from January 2019 to September 2020 found a slight decrease in incidence of AD prescriptions in both sexes and in all age groups during the outbreak, using electronic data provided by a large number of GPs (Carr et al., 2021). Similarly, a German study found a decrease in AD prescriptions comparing the first six-months of 2020 with those of 2019, in subjects diagnosed with anxiety disorders (Jacob et al., 2020). In a report from the Italian Drugs' Agency, data on AD use at the country-level in March and April 2020 did not show significant differences when compared to January and February of the same year (Agenzia Italiana del Farmaco, 2020). A study from Tuscany showed an increase of AD use from June 2020, while a reduction was observed in the first lockdown, in contrast with our findings (Antonazzo et al., 2022). It is a fact, however, that the COVID-19 has affected population well-being due to the consequences of the lockdown restrictions, the discontinuation or alteration of working activities, and, to a certain extent, the financial, relational, or housing problems. This could have resulted in a rise in anxiety, depressive and sleeping disorders in Italy and internationally (Castellini et al., 2021; Cellini et al., 2020; Gualano et al., 2020; Mazza et al., 2020; Pierce et al., 2020; Rossi et al., 2020; Winkler et al., 2021). It would be important, thus, to assess if this rise may have contributed to an increase of AD prescriptions in other areas using longer observational periods after the first wave of the pandemic (Antonazzo et al., 2022; Castellini et al., 2021; Rabeea et al., 2021).
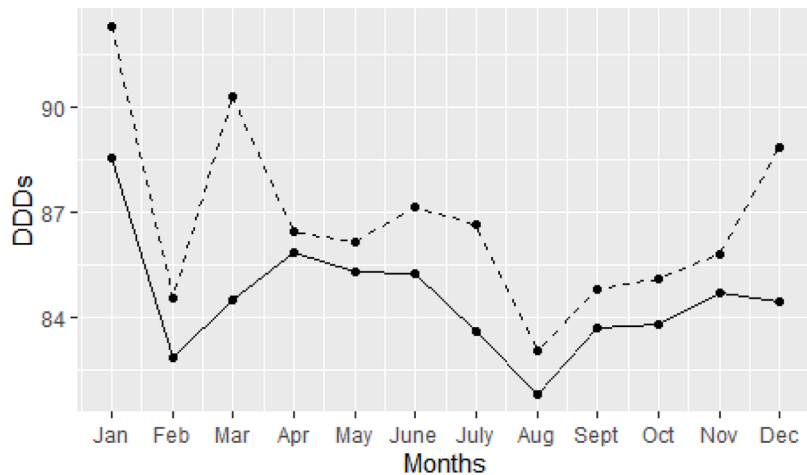
Fig. 1. Monthly means of predicted and observed defined daily doses (DDDs) in 2020 overall for all antidepressants (ADs).
Dashed line = monthly means of observed number of DDDs in 2020; solid line = monthly means of predicted number of DDDs for 2020 based on AD data from 2015 to2019.
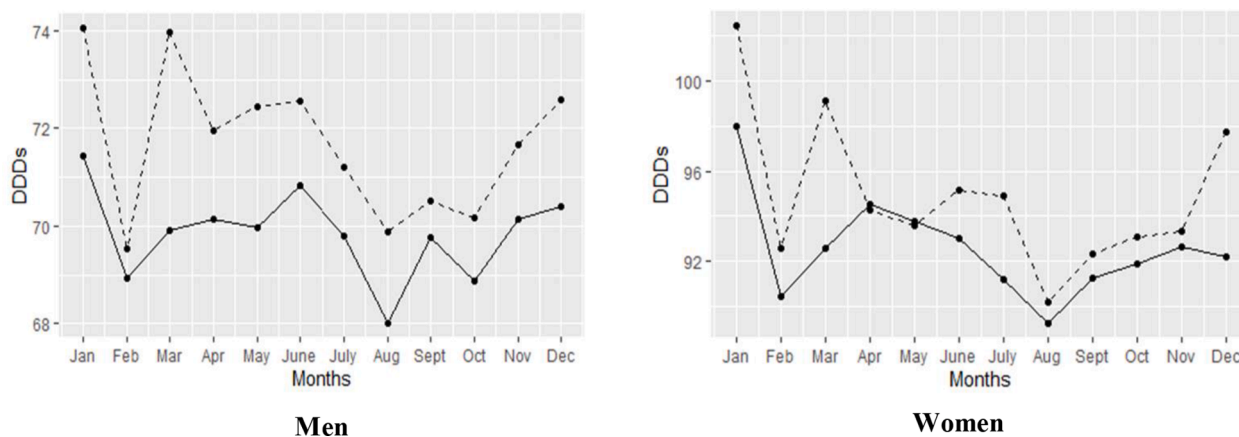

Men

Women

Fig. 2. Monthly means of predicted and observed defined daily doses (DDDs) in 2020 by sex for all antidepressants (ADs).
Dashed line = monthly means of observed number of DDDs in 2020; solid line = monthly means of predicted number of DDDs for 2020 based on AD data from 2015 to2019.

When comparing the periods 2015–2019 and 2020 this study showed that the use of ADs increased similarly in the two sexes, but the monthly means of the observed DDDs were higher than the predicted particularly among men. Men, thus, might have been more affected by pandemic consequences, which may have led to mental distress and a consequent higher use of ADs during all the outbreak period. However, Italian studies reported a greater extent of psychological problems among women during the pandemic (Gualano et al., 2020; Mazza et al., 2020; Rossi et al., 2020), which may be corroborated by the fact that women received more than 70% of ADs dispensed and a rise of AD use in women during the pandemic was also observed in comparison to previous years.

We found the highest increase in AD use in young people, especially men, which may be in line with other studies suggesting a higher burden of mental distress due to the pandemic at this age (Pierce et al., 2020; Winkler et al., 2021). When comparing observed AD use in 2020 with predicted, however, young age group did not show a clear increased pattern. On the other hand, it should be noticed that older age groups were dispensed the great majority of ADs, and adults aged 30-59 received higher amount of ADs than predicted in all months of 2020, which could suggest the possibility that this age group has broadly suffered from work-related troubles or economic damage due to the pandemic (Gualano et al., 2020; Mazza et al., 2020; Rossi et al., 2020).

The most pronounced rise of AD use was observed in the first four months of 2020, with a peak of more than 40% in March 2020. After-wards, we observed a second pronounced increase in November and December. These periods correspond with the months before the beginning and during the early periods of the first and the second strict lockdowns in Italy. This is in line with the possibility of a hoarding of electronic repeated prescriptions in preparation and during the early phase of the first lockdown, due also to the fear of a shortage of medications (Carr et al., 2021; Karlsson et al., 2021), since the duration and severity of restrictions were unclear. Findings from Tuscany also showed an increase of AD prevalence at the end of February 2020, in line with this hypothesis. In contrast, the same study found a reduction of AD use during the first lockdown (Antonazzo et al., 2022). Although the reason is difficult to assess, one may speculate that Italian healthcare system differs by region, and these differences became particularly prominent with regard to mental care in FVG during the first lockdown period. Although in other areas of Italy a substantial reduction of psychiatric services' seeking was observed, this was less likely in the strongly community-based mental care of FVG (Castelpietra et al., 2020). The hoarding during the lockdown in November and December 2020, which was less strict than the first one might be mainly linked to an increase of common mental disorders and an increase of psychiatric assessments after the first lockdown (Balestrieri et al., 2021; Beghi et al., 2022). The Tuscan study also reported an increase in the incidence of AD
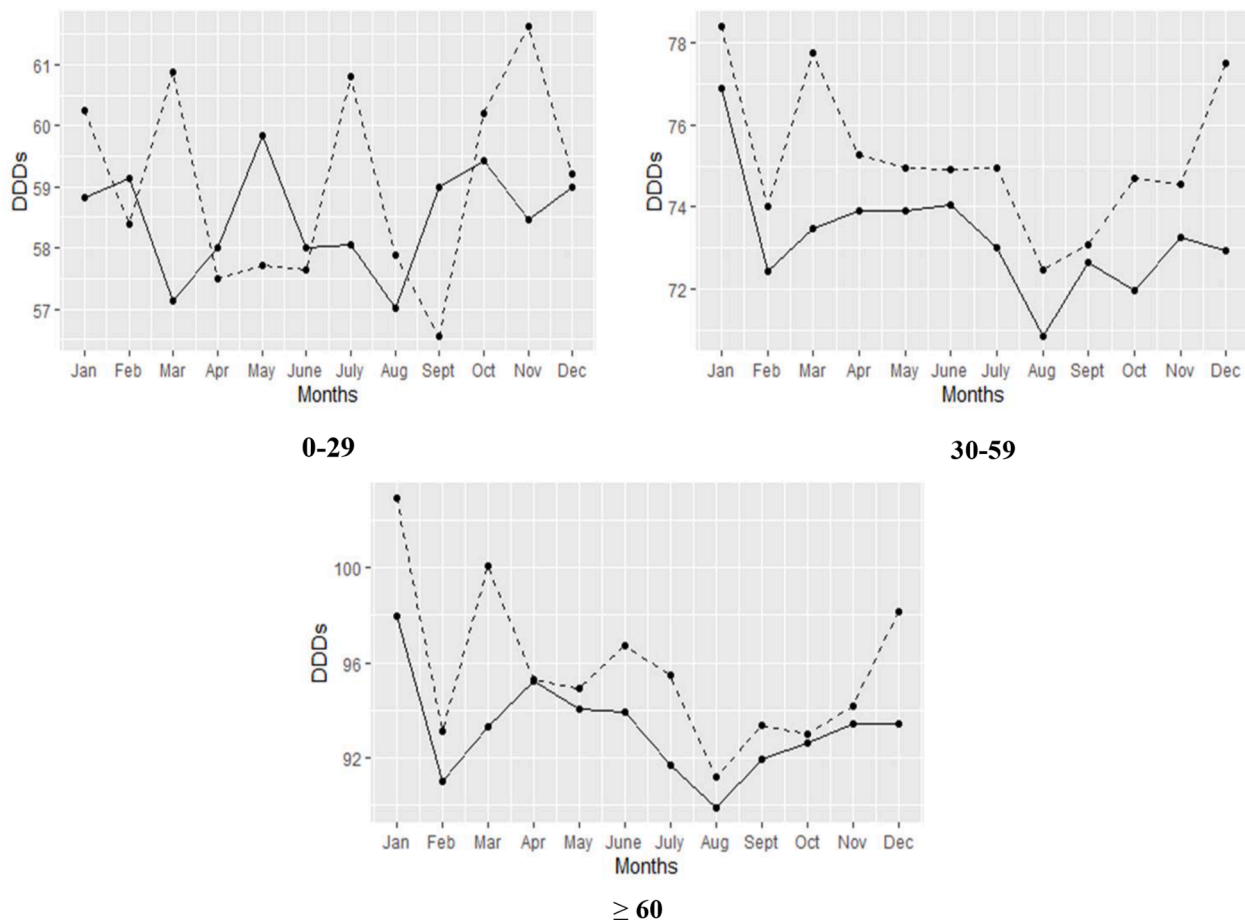
0-29

30-59

≥ 60

Fig. 3. Monthly means of predicted and observed defined daily doses (DDDs) in 2020 by age groups for all antidepressants (ADs).
Dashed line = monthly means of observed number of DDDs in 2020; solid line = monthly means of predicted number of DDDs for 2020 based on AD data from 2015 to2019.

prescriptions during the second-half of 2020 (Antonazzo et al., 2022), corroborating our findings. It should be noticed, however, that an increasing trend in AD use among subjects with depression was observed in the pre-pandemic period among European countries (Chen et al., 2022). This may have diluted the direct effect of the pandemic on AD prescriptions, in particular at the beginning of 2020, when the increase is unlikely explained by an increase of depression or anxiety.

The group of other ADs, (including mirtazapine and trazodone), showed an increase of more than 30% in 2020. This may be due to a higher incidence of sleeping disturbances during the Italian lockdown, for which these drugs are broadly used (Castelpietra et al., 2017). In contrast, TCAs showed no increase, possibly due to both their common use for pain disorders (Trifiro et al., 2013), and that GPs are less likely to prescribe TCAs for psychiatric conditions, because of their lower safety compared to newer ADs (Castelpietra et al., 2019).

4.1. Strengths and limitations

The main strength of this study is that it uses population-level data, stratified by sex, age, and AD class. To our knowledge, this is the first Italian study, and one of the few at the global level, analysing AD use during the first year of the COVID-19 pandemic in comparison with the previous five-year period also stratifying the analyses on sex, age of AD users and AD class. A number of limitations, however, should be considered. Firstly, the anonymization of data prevented the identification of AD use at individual level over time. Secondly, only AD prescriptions issued by GPs, psychiatrists, and other public physicians were available from the register, albeit this represents 90% of the

prescriptions (Castelpietra et al., 2015). Thirdly, we were not able to assess the adherence to ADs, a common limitation of studies based on prescription registers (Castelpietra et al., 2019; Castelpietra et al., 2017; Rabeea et al., 2021). Fourthly, we could not adjust the analyses for other factors, such as socioeconomic status or psychiatric diagnoses.

5. Conclusions

The observed 20% increase in AD prescriptions may be related to a rise in mental problems of the general population due to the COVID-19 consequences, in particular anxiety, depression and sleeping disturbances. Moreover, it is likely that this increasing trend was not due to the rise in AD prescriptions observed in Italy in the pre-COVID period, since the observed number of DDDs dispensed was also higher than the predicted. The increase might be further related to a hoarding of prescriptions before and during the early phases of lockdown restrictions, which could have been reflected in the prescriptions' peak in particular during the first months of the pandemic. Future research, may focus on the use of AD at the individual level, to provide more information on indication for AD treatment and on other characteristics, including socioeconomic status and psychological risk-factors related to the pandemic consequences.
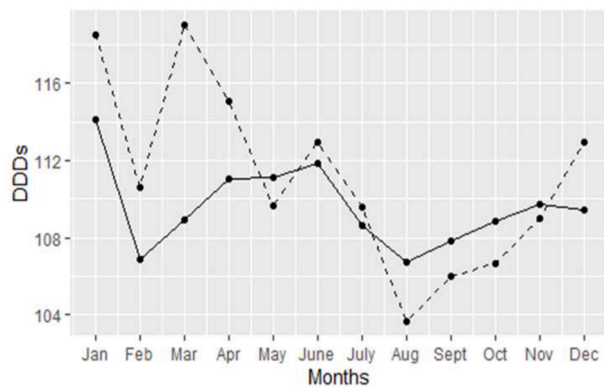
Author Contribution

LP and GC conceptualised, designed and led the study, with assistance from JR. GC and JR conducted the internet searches for literature. LE, GZ and AP were responsible for data verification, management and
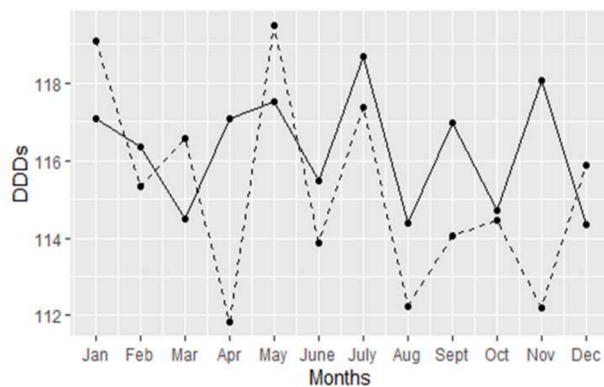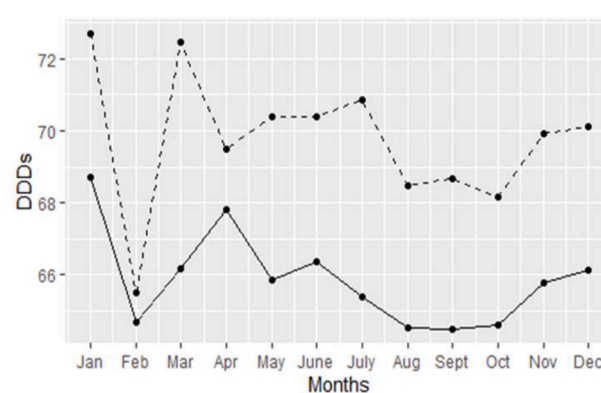
TCA
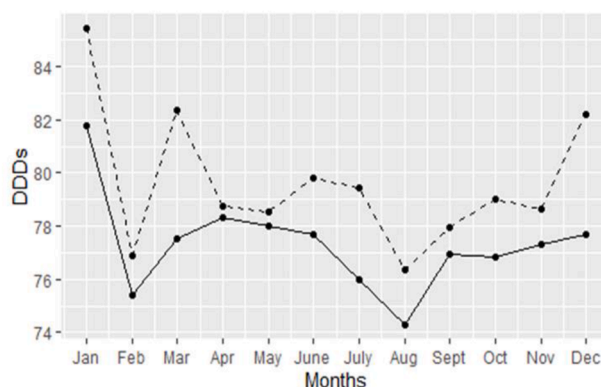
SSRI

SNRI

Other ADs

Fig. 4. Monthly means of predicted and observed defined daily doses (DDDs) in 2020 by antidepressant (AD) classes.
Dashed line = monthly means of observed number of DDDs in 2020; solid line = monthly means of predicted number of DDDs for 2020 based on AD data from 2015 to 2019.

storage. LP did the statistical analysis. LP and GC prepared the first draft of the manuscript with input from JR. All authors interpreted data and made critical intellectual revisions to the manuscript.

Declaration of Competing Interest

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