Prescription of anxiolytics, sedatives, hypnotics and antidepressants in outpatient, universal care during the COVID-19 pandemic in Portugal: a nationwide, interrupted time-series approach

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ABSTRACT

Background The COVID-19 pandemic has had a significant impact on the population's mental health. However, its impact on the consumption of anxiolytics, sedatives, hypnotics and antidepressants remains to be evaluated. Hence, this article aims to assess the prescription trends of these drugs in Portugal, from January 2018 to March 2021, while critically examining whether the COVID-19 pandemic had an impact on these prescription trends or not.

Methods A nationwide interrupted time-series analysis of the prescription data of anxiolytics, sedatives, hypnotics and antidepressants in outpatient setting of the public health sector was conducted. The data encompassed the defined daily dose per month, age range and sex and were analysed following a segmented regression approach.

Results The pandemic preceded an immediate reduction in the prescription of anxiolytics, sedatives and hypnotics for children and adolescents. However, an increasing trend throughout the pandemic has been noted in the prescription of these drugs, especially among adults aged 65 years or above. A drop in antidepressant prescription was observed as an immediate effect of the pandemic among male and female adolescents and elderly women. From March 2020 to March 2021, a decreasing prescription trend has been noted among men.

Conclusions When analysing specific genders and age ranges, differences can be noted, in terms of both immediate impact and prescribing trends throughout 1 year of the COVID-19 pandemic. The impact of the pandemic on mental health and its association with the consumption trends of psychoactive drugs, and with the access to mental health treatments, should be further assessed.

INTRODUCTION

Since 31 December 2019, the COVID-19 epidemic has escalated and quickly spread around the world. The WHO formally declared the existence of a pandemic in March 2020,[1] with the first confirmed case in Portugal occurring on 2 March 2020.[2] Portugal was one of the countries that adopted earlier containment measures, reaching a peak in the number of newly confirmed cases on 10 April 2020[2] while always presenting lower fatality rates than the European average. The declaration of the state of emergency in Portugal was decreed on 18 March, along with several measures to reduce the risk of contracting and transmitting COVID-19, such as closing university campuses, prohibiting large gatherings and announcing mandatory confinement at home.[3] After the first wave and the subsequent deconfinement, a new declaration of the state of emergency was decreed on 6 November,[4] reaching a peak of incidence on 19 November, with a 7-day rolling average incidence of 630 cases/1 000 000 inhabitants. After a slight reduction in the number of cases during November–December 2020, a third wave followed during January 2021, reaching an unprecedented incidence of COVID-19 cases, with a 7-day rolling average of 1264 cases/1 000 000 inhabitants.[2]

Further than the stresses characteristic of the illness itself, mass home-confinement directives were unprecedented, raising concerns about their impact on the population.[5] The increase in mental distress and mental disorders may have occurred not only among those who suffered from COVID-19 but also among quarantined people in general and health practitioners.[5] People with mental health disorders are generally more susceptible to infection during epidemics, and it appears that there is a bidirectional association between psychiatric disorders and COVID-19. Psychiatric disorders appear to be an independent risk factor for COVID-19, and survivors of COVID-19 disease are at an increased risk of psychiatric sequelae.[6 7] A recent US study reported a rise in antidepressant, anti-anxiety and anti-insomnia drug prescription since the reporting of the first COVID-19 cases in mid-February 2020, peaking on the second week of March, when COVID-19 was declared a pandemic by the WHO.[1 8]

In Portugal, mental disorders are associated with one of the highest societal costs in high-income countries, causing more than 20% of unproductive days.[9 10] Yet, despite the high prevalence of these disorders, the period between the disease onset and the initiation of therapy remains concerning.[11] Furthermore, poor access to prompt non-pharmacological therapy within

the Portuguese National Health System (NHS) may explain the increasing consumption of anxiolytics, sedatives, hypnotics and antidepressants.[12]

As women and elders tend to be more vulnerable to common mental health disorders, such as depression and anxiety, they are among the groups that most consume anxiolytics, sedatives, hypnotics and antidepressants.[10 12] During the COVID-19 pandemic, women and adolescents were shown to be among the most vulnerable groups in terms of mental health, while older adults have experienced a slight improvement in their mental health during the first months of the pandemic.[13–17] The main objectives of this study are to (1) evaluate the prescription trends of anxiolytics, sedatives, hypnotics and antidepressants, in outpatient setting in Portugal, from January 2018 to March 2021 and to (2) verify whether the COVID-19 pandemic had an impact on the aforementioned prescription trends.

MATERIALS AND METHODS

Setting

Portugal has a population of around 10.3 million inhabitants[18] unevenly distributed, with a high incidence in the metropolitan areas of Lisbon and Oporto. The NHS is a universal tax-financed system tendentially free-of-charge covering all residents in Portugal.[19] The NHS does not cover all prescribed medication. Antidepressants, anxiolytics, sedatives and hypnotics are subject to variable patient coinsurance with a co-payment rate of 37% of the price, corresponding to non-priority medicines with proven therapeutic value,[20] and are dispensed in pharmacies only when a medical prescription is presented.[19]

Study design and data collection

We used an uncontrolled interrupted time-series (ITS) design with monthly data, from January 2018 to March 2021.[21] This design allows for effects to be estimated by controlling for baseline levels and trends. The data concerning drug prescription were obtained from the System of Information and Monitoring of the Portuguese NHS public-access platform, between January 2018 and March 2021. This platform was developed by the shared services of the Health Ministry (Serviços Partilhados do Ministério da Saúde) and aims to strengthen, integrate and aggregate medical/health data on a national scale.[22] As the platform included the prescription by several institutions, the following were excluded: health institutions associated with Ministries other than the Health Ministry, administrative institutions of the National Health Service and addiction rehabilitation centres.

The data on prescription collected comprised the monthly defined daily dose (DDD) of anxiolytics, sedatives and hypnotics, and antidepressants (Anatomical Therapeutic Chemical (ATC) codes N05B, N05C and N06A, respectively) prescribed in outpatient settings by physicians of the public health sector (including hospitals, hospitals centres and primary care centres/units), across the period January 2018 to March 2021. Data were stratified by sex and age range. Although the United Nations and the WHO defined specific age ranges, the database only allowed the stratification by the following intervals: 0–7 years old (childhood), 8–17 (adolescence), 18–64 (adults), 65–74 (older adulthood) and 75+ (elderly).[23 24]

The target drugs of this study were the classes corresponding to the ATC codes N05B (anxiolytics), N05C (sedatives and hypnotics) and N06A (antidepressants). At the same time, at the national level, there is also a pharmacotherapeutic classification. This classification of medicines is carried out based on a systematisation grouped according to their identity and the therapeutic indications for which they are approved and authorised.[25] As the national drug classification merges N05B and N05C into one category, the data obtained are then presented into two main variables: anxiolytics, sedatives and hypnotics (N05B+N05C), and antidepressants (N06A). This study is reported as per the Reporting of studies Conducted using Observational Routinely collected health Data statement[26] (see online supplemental material S1).

Statistical analysis

An ITS analysis model based on a segmented regression approach[27–29] was designed to analyse the differences between the monthly prescribed DDDs of anxiolytics, sedatives, and hypnotics and antidepressants. A segmented linear regression analysis model[30] was designed to analyse the differences observed between March 2020 and March 2021, in terms of prescribed drugs. For statistical analysis purposes, we constructed a segmented regression model of the ITS for each outcome analysed: monthly prescribed DDDs of (1) anxiolytics, sedatives and hypnotics and (2) antidepressants. The independent variables were defined as follows: time (t:1, 2, 3…, 39), a binary variable (COVID-19) taking values of '0' before March 2020 and '1' since March 2020, corresponding to the time in which the effect of the pandemic is measured, and a variable for the time elapsed since the first COVID-19 case, which took the value of '0' before and values of '1', '2', '3', …, corresponding to the months from March 2020 to March 2021. To identify possible seasonal changes in antibiotic prescribing, the X-13 ARIMA (autoregressive integrated moving average)-SEATS procedure was applied.[31] This method is an adaptation of the US Bureau of the Census X-13-ARIMA model that produces a seasonally adjusted time-series. The Cumby-Huizinga test was used to check for autocorrelation (10 lags of autocorrelation were tested). Based on the results of these tests, we introduced lags of the dependent variable to correct for autocorrelation. Sensitivity analyses that vary the timing of pandemic interruption in plus and minus a month for all ITS models were performed. This analysis allows to see how coefficients change and the robustness of the results. The normality of the outcomes was confirmed by the Kolmogorov-Smirnov test ($p>0.1$). All analyses were performed using the free R statistical software environment (V.4.0.5),[32] except the Cumby-Huizinga test that was carried out with Stata V.12.[33]

RESULTS

Prescription trends of anxiolytics, sedatives, hypnotics and antidepressants

When analysing the prescription trends of anxiolytics, sedatives and hypnotics throughout January 2018 to March 2021, no significant alterations have been noted in any of the groups considered. On the contrary, apart from children, all other groups revealed a significant increase in the prescription of antidepressants throughout the period under study (see online supplemental material S2).

The impact of the COVID-19 pandemic on the prescription of anxiolytics, sedatives and hypnotics

Figure 1 displays the prescription tendencies among male and female patients. A sharp decline can be noticed at the beginning of the pandemic. However, when considering the period from March 2020 to March 2021, an increasing tendency is observed. The prescription of these drugs has

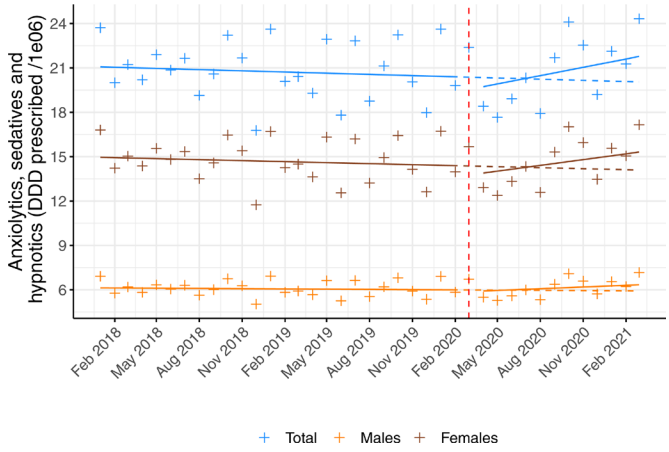

Figure 1 Anxiolytics, sedatives, and hypnotics monthly prescribing per gender. (Blue, brown and orange lines (–): trend line, after model adjustment; Blue, brown and orange dashed lines: counterfactual; Red dashed line: COVID-19 emergence (March 2020)). DDD, defined daily dose.

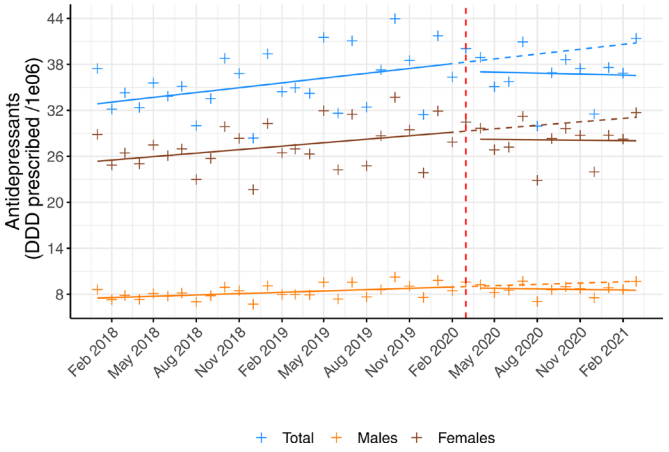

Figure 2 Antidepressants monthly prescribing per gender. (Blue, brown and orange lines (–): trend line, after model adjustment; Blue, brown and orange dashed lines: counterfactual; Red dashed line: COVID-19 emergence (March 2020)). DDD, defined daily dose.

remained almost three times higher among female patients compared to male patients after the beginning of the pandemic.

The results displayed in table 1 show a significant, immediate reduction in the prescription of anxiolytics, sedatives and hypnotics on male and female children (B=−3795.81 and B=−2938.74, respectively), adolescents (B=−2899.09 and B=−7142.78, respectively) and elderly women (B=−330 938.28). In terms of relative change, a drop in the prescription of these drugs by almost 50% has been noted among children, and a decrease by 10.57% and 27.46% has been observed among male and female adolescents, respectively. No immediate impact has been observed on any other group. However, an overall increasing prescription trend has been noted throughout the COVID-19 pandemic (B=185 245.64), especially among male and female older adults (B=13 162.11 and B=40 328.93, respectively) and the elderly (B=14 582.46 and B=55 986.34, respectively). The adjusted coefficients are presented in the supplementary material (see online supplemental material S2).

The impact of the COVID-19 pandemic on the prescription of antidepressants

The figure 2 displays the prescription tendencies among male and female patients. Until the beginning of the pandemic, an increasing trend was observed but since then, a decreasing tendency was apparent. Again, the prescription of these drugs is more than three times higher among female patients compared to male patients.

A significant, immediate impact of the COVID-19 pandemic on prescription of antidepressants has been noted among male and female adolescents (B=−9808.52 and B=−20 817.58, respectively) and elderly women (B=−293 440.34), as shown in table 2. However, when analysing the relative change a month after the pandemic emerged, the children and adolescent groups have experienced the most pronounced drop in the prescription of antidepressants, ranging from 8% to 23%. During the period corresponding to March 2020 to March 2021, a decreasing trend can be noted in male adolescents (B=−2313.24), adults (B=−37 988.11), older adults (B=−18 402.10) and the elderly (B=−17 232.59). No significant impact of the COVID-19 pandemic has

Table 1 Segmented regression of time-series results expressed in defined daily doses—prescription of anxiolytics, sedatives and hypnotics

	Immediate impact		Change in trend		Absolute change in outcome a month after COVID-19	Relative change in outcome a month after COVID-19 (%)
	B	95% CI	B	95% CI		
Male						
Children (≥7 yo)	−3795.81*	−5361.47 to −2230.15	−0.36	−179.70 to 178.99	−3796.17	−47.60
Adolescents (8–17 yo)	−2899.09*	−5673.12 to −125.05	122.73	−188.30 to 433.77	−2776.35	−10.57
Adults (18–64 yo)	−168 291.27	−439 366.75 to 102 784.21	27 129.40	−3468.68 to 57 727.48	−141 161.87	−5.74
Older adults (65–74 yo)	−34 403.70	−100 896.53 to 32 089.14	13 162.11*	4929.03 to 21 395.18	−21 241.59	−1.58
Elderly (≥75 yo)	−30 939.04	−94 317.29 to 32 439.20	14 582.46*	6863.67 to 22 301.26	−16 356.58	−1.25
Female						
Children (≥7 yo)	−2938.74*	−3966.10 to −1911.38	−26.05	−133.60 to 81.50	−2964.79	−47.82
Adolescents (8–17 yo)	−7142.78*	−12 399.81 to −1885.75	521.04	−5.99 to 1048.07	−6621.74	−27.46
Adults (18–64 yo)	−80 580.27	−676 807.98 to 515 647.44	45 887.32	−23 833.17 to 115 607.81	−34 692.95	−0.77
Older adults (65–74 yo)	−186 383.98	−374 446.64 to 1678.67	40 328.93*	17 743.87 to 62 913.98	−146 055.06	−4.50
Elderly (≥75 yo)	−330 938.28*	−516 988.89 to −144887.66	55 986.34*	34 033.34 to 77 939.34	−274 951.94	−7.20
Total	−724 445.94	−1 881 469.52 to 432 577.63	185 245.64*	40 314.44 to 330 176.85	−539 200.30	−3.37

The impact of the COVID-19 pandemic on the prescription of antidepressants.
*p<0.05

Table 2 Segmented regression of time-series results expressed in defined daily doses—prescription of antidepressants

	Immediate impact		Change in trend		Absolute change in outcome a month after COVID-19	Relative change in outcome a month after COVID-19 (%)
	B	95% CI	B	95% CI		
Male						
Children (≥7 yo)	−131.65	−439.62 to 176.32	−12.17	−47.23 to 22.90	−143.82	−23.23
Adolescents (8–17 yo)	−9808.52*	−180 70.96 to −1546.07	−2313.24*	−3982.57 to −643.90	−12 121.75	−8.47
Adults (18–64 yo)	−99 413.19	−325 900.12 to 127 073.73	−37 988.11*	−73 488.17 to −2488.06	−137 401.30	−3.37
Older adults (65–74 yo)	−21 996.52	−112 863.08 to 68 870.04	−18 402.10*	−33 121.97 to −3682.23	−40 398.63	−1.92
Elderly (≥75 yo)	−17 503.89	−122 518.89 to 87 511.12	−17 232.59*	−31 880.87 to −2584.30	−34 736.47	−1.57
Female						
Children (≥7 yo)	−0.14	−0.48 to 0.20	0.01	−0.03 to 0.05	−0.13	−8.72
Adolescents (8–17 yo)	−20817.58*	−33 061.47 to −8573.69	−404.13	−1967.06 to 1158.79	−21 221.71	−16.94
Adults (18–64 yo)	−383 600.69	−1 156 313.53 to 389 112.14	−91 526.60	−201 911.88 to 18 858.67	−475 127.30	−3.25
Older adults (65–74 yo)	−218 185.26	−460 427.56 to 24 057.05	−24 970.70	−61 175.54 to 11 234.14	−243 155.96	−3.99
Elderly (≥75 yo)	−293 440.34*	−546 313.17 to −40 567.51	−22 566.81	−59 314.21 to 14 180.60	−316 007.15	−5.34
Total	−982 713.66	−2 593 215.55 to 627 788.23	−200 913.88	−441 477.53 to 39 649.77)	−1 183 627.54	**−3.55**

*p<0.05

been observed in the prescription of antidepressants among female patients. The adjusted coefficients are presented in the supplementary material (see online supplemental material S3).

Sensitivity analysis

The results of the sensitivity analysis are presented in Supplemental Material (see online supplemental materials 4 and 5). All specifications show very similar results, despite slight changes in magnitude and statistical significance in some coefficients; hence, the conclusions inferred from the obtained results remain unchanged.

DISCUSSION

To our knowledge, this is the first study concerning the prescription of anxiolytics, sedatives, hypnotics and antidepressants within the Portuguese NHS throughout 1 year of the COVID-19 pandemic using IHS.

Main results

The COVID-19 pandemic has preceded an immediate reduction in the prescription of anxiolytics, sedatives and hypnotics, especially among children, adolescents and elderly women. Furthermore, a reduction in antidepressant prescription has also been noted among adolescents and elderly women. Throughout the period of the COVID-19 pandemic, statistically significant decreases were observed in the prescription of antidepressants among male patients. On the contrary, significant increasing trends in the prescription of anxiolytics, sedatives and hypnotics were observed among women aged 65 years or above. Thus, an amplification of the discrepancies in prescription between male and female patients has been observed.

Prescription of anxiolytics, sedatives and hypnotics

A significant decrease in the prescription of anxiolytics, sedatives and hypnotics for children and adolescents was noted. This might be a result of the decreased number of doctor visits during the first months of the COVID-19 pandemic,[34] as these drugs are only provided through medical prescription. Yet, careful considerations should be made when associating these decreasing trends with the mental state of children and adolescents during the COVID-19 pandemic, as recent literature reports increasing mental distress on these populations and a doubling of prevalence rates of anxiety and depressive symptoms, as a result of the disruption of routines, social distancing and confinement.[5 35–37] Thus, the decreasing consumption of these drugs does not reflect the increasingly damaged mental health of younger people, which raises concerns regarding access to paediatric mental healthcare during the pandemic, especially among girls.[37] . The initial decrease in prescriptions was followed by a non-significant growth, which might reflect a slow returning to previous patterns. On the contrary, stringent confinement measures might have had a protective effect on the mental health of children and adolescents that often have increased stress levels at school—caused by bullying, direct confrontation with teachers and peers, concerns about the physical appearance, integration among peers—which can also explain the decreasing trends in prescription among these groups.

A sharp reduction in the prescription of these drugs has been also observed as an immediate impact of the COVID-19 pandemic among elderly women, which, along with the decreasing number of doctor visits,[34] might be associated with the improvement—or stabilisation—of the mental state of older adults during the first months of the COVID-19 pandemic.[13 14 38] However, an increasing trend has been noted among older adults and the elderly throughout 1 year of the COVID-19 pandemic, which, despite the short-term resilience of these patients, highlights the concerns regarding the long-term impact on the mental health of patients aged 65 years or above.[13]

Antidepressant prescription

Although an increasing trend in the prescription of antidepressants can be noted throughout the period prior to the pandemic,[12] an immediate decrease in prescription is noted among adolescents and elderly women, which, similar to the prescription of anxiolytics, sedatives and hypnotics, might be associated with the decreased number of doctor visits and improvement in the mental health of the elderly.[34 38 39]

A significant decreasing tendency has been observed since the pandemic began among male patients. No significant changes during this period have been noted on female patients. This

What is already known on this subject

- The COVID-19 pandemic has been associated with increased mental distress in the population.
- Portugal is one of the European countries that consumes a higher number of mental health-related drugs.
- Considering the impact of these unprecedented times on mental health, it is crucial to analyse the impact of the pandemic on the prescription of these drugs in Portugal.

What this study adds

- This study, with an interrupted time-series design, analyses the prescription trends during the first 9 months of the COVID-19 pandemic, stratifying data by sex and age range.
- A reduction in the prescription of anxiolytics, sedatives and hypnotics has been noted as an immediate impact of the COVID-19 pandemic on children, adolescents and elderly women. An overall increase in prescription in the subsequent months was noted among adults aged 65 years or above.
- The prescription of antidepressants has significantly declined throughout the pandemic among male patients aged 8 years and above.

declining trend throughout the pandemic months among men might be a reflex of the slow returning to previous tendencies and loosening of containment measures.[3] Yet, increasing prescription tendencies of antidepressants before the beginning of the pandemic were observed, and increasing mental distress during the pandemic has been reported,[36 40] especially among women.[15 16 41] Hence, our results might incite reflection on whether the pandemic has been an obstacle for the treatment of people with depressive disorders, as avoidance of medical care out of COVID-19-related concerns has been reported.[42 43]

Study limitations

This study reveals a distinctive approach to the consumption of mental health-related drugs during the pandemic but has, however, some limitations. The information obtained reports only monthly data, so the impact of specific days cannot be determined, such as the declaration of the state of emergency, which occurred in mid-March 2020. Furthermore, the data extracted only correspond to prescribed drugs in the public sector, which might not reflect the actual consumption of these drugs and does not reflect the prescriptions on the private health sector throughout the months considered. Regarding the statistical analysis, the models assume a linear trend in the outcome within each segment, and changes may follow non-linear patterns. In addition, the assumption of linearity may hold only over short intervals.

CONCLUSIONS

As these results offer an overview of the impact of the pandemic from a pharmacoepidemiological standpoint, it is now important to assess whether the prescription of anxiolytics, sedatives and hypnotics, as well as of antidepressants, is related to an impact on mental health disorders from a clinical standpoint. Despite our results, the mental health of the population should be carefully monitored, for instance, with measures to tackle the impact of the pandemic on the mental health of the population, especially considering previous reports pointing to a rise in the incidence of mental health disorders on COVID-19 emergence.[44] Further studies could complement the results obtained with the follow-up of future prescription trends.

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