MEDS

The impact of COVID-19 pandemic on alcohol dependence treatment in Portugal

Débora Filipa Araújo Figueira

MESTRADO EM
EVIDÊNCIA E DECISÃO EM SAÚDE
2º CICLO DE ESTUDOS

SET|2023

U. FMUP

MEDS

The impact of COVID-19 pandemic on alcohol dependence treatment in Portugal

Débora Filipa Araújo Figueira

MESTRADO EM
EVIDÊNCIA E DECISÃO EM SAÚDE
2º CICLO DE ESTUDOS

ORIENTADORES:

Bernardo Sousa Pinto (FMUP e CINTESIS)

António Teixeira Rodrigues (ANF e Universidade do Minho)

SET|2023

FMUP

Abstract

Introduction: The COVID-19 pandemic imposed significant risks to marginalised people, particularly those with substance abuse disorders. In 2019, Portugal, total alcohol consumption, per capita in adults was 12.1 L/year of pure alcohol, which is higher than the European average (9.5 L/year of pure alcohol). Pharmacological treatment of alcohol use disorders can reduce relapse, cravings, drinking frequency, and negative symptoms that occur immediately after alcohol withdrawal. Despite the positive outcomes of alcohol dependence treatment, a low rate of patients remains on treatment.

Aim: To estimate the impact of COVID-19 pandemic on persistence to alcohol dependence treatment in Portugal.

Methods: Retrospective cohort study of patients with a dispense of acamprosate, disulfiram, nalmephen or naltrexone in the Portuguese community pharmacies. Medicine's sales data for the period between January of 2019 and March of 2022 were retrieved. Kaplan-Meier survival analysis was used to estimate patients' persistence to treatment. Hazard ratios were estimated using a Cox proportional hazard model.

Results: The study findings showed that, COVID-19 was significantly associated with an increased risk of treatment non-persistence with disulfiram (HR: 1.10; 95% CI: 1.01 to 1.19, $p=0.032$), nalmephen (HR: 1.40; 95% CI: 1.18 to 1.66, $p<0.001$) and naltrexone (HR: 1.20; 95% CI: 1.11 to 1.30, $p<0.001$). Regarding acamprosate, in the first 90 days of treatment, the pandemic was associated with an increased risk of non-persistence to this medicine (HR: 1.08; 95% CI: 1.00 to 1.16, $p=0.044$). However, after 90 days of treatment, COVID-19 seems to have a protective impact, reducing the risk of treatment non-persistence (HR: 0.74; 95% CI: 0.65 to 0.85, $p<0.001$).

Discussion: COVID-19 have affected patients' persistence to alcohol dependence treatment. During an epidemic is expected a similar trend in other therapeutical areas as this resulted from the difficult access to health care services during this period. Preventive measures should be taken in future epidemics to reduce the risk of treatment non-persistence.
Keywords: COVID-19, treatment persistence, alcohol dependence, real-world data, pharmacy.

Resumo

Introdução: A pandemia de COVID-19 impôs riscos significativos a indivíduos marginalizados, particularmente aqueles com transtornos por abuso de substâncias. Em 2019, em Portugal, o consumo total de álcool *per capita* em adultos foi de 12,1 L/ano de álcool puro, valor superior à média europeia (9,5 L/ano de álcool puro). O tratamento farmacológico da dependência de álcool pode reduzir a recaída, os desejos, a frequência de consumo, assim como os sintomas negativos que ocorrem imediatamente após a abstinência. Apesar dos resultados positivos do tratamento da dependência de álcool, uma proporção reduzida de indivíduos permanece em tratamento.

Objetivos: Estimar o impacto da pandemia de COVID-19 na persistência ao tratamento da dependência de álcool em Portugal.

Métodos: Estudo de coorte retrospetivo de doentes com dispensa de acamprosato, dissulfiram, nalmefeno ou naltrexona nas farmácias comunitárias portuguesas. Os dados de vendas de medicamentos foram recolhidos para o período entre janeiro de 2019 e março de 2022. A persistência dos doentes ao tratamento foi estimada por análise de sobrevivência segundo o método de *Kaplan-Meier*. A razão de riscos (hazard ratio) foi estimada através de um modelo de risco proporcional de Cox.

Resultados: Os resultados do estudo mostraram que a COVID-19 se associou a um aumento significativo do risco de não persistência ao tratamento com dissulfiram (HR: 1,10; IC 95%: 1,01 a 1,19, p=0,032), nalmefeno (HR: 1,40; IC 95%: 1,18 a 1,66, p<0,001) e naltrexona (HR: 1,20; IC 95%: 1,11 a 1,30, p<0,001). Quanto ao acamprosato, até aos 90 dias de tratamento, a pandemia associou-se a um aumento do risco de não persistência ao tratamento (HR: 1,08; IC 95%: 1,00 a 1,16, p=0,044). No entanto, após 90 dias de tratamento, a COVID-19

parece ter um impacto protetor, reduzindo o risco de não persistência ao tratamento (HR: 0,74; IC 95%: 0,65 a 0,85, p<0,001).
Discussão: A COVID-19 afetou a persistência dos doentes ao tratamento da dependência de álcool. Durante uma epidemia é expectável um comportamento semelhante em outras áreas terapêuticas, devido ao difícil acesso aos serviços de saúde durante esse período. Em futuras epidemias, deverão ser adotadas medidas preventivas para reduzir o risco de descontinuação do tratamento.
Palavras-chave: COVID-19, persistência do tratamento, dependência de álcool, dados do mundo real, farmácia.

Acklowledgments

I would like to thank to António Teixeira Rodrigues who encouraged me to deepen my knowledge at the beginning of my career and who guided me in the development and elaboration of this project. To José Pedro Guerreiro who was always available to help me. To Professor Bernardo Sousa Pinto for his advice and guidance. To Professor Matilde Soares who throughout the last year gave me the necessary push to complete this project. To my friends and family for their unconditional support.

My sincere gratitude.

Table of contents

Abstract ..... **iii**

Resumo ..... **v**

Acklowledgments ..... **vii**

Table of contents ..... **viii**

Acronyms and abbreviations ..... **ix**

List of figures ..... **x**

List of tables ..... **xi**

1. Rationale **13**

2. Material and Methods **19**

3. Results **22**

4. Discussion **32**

5. References **36**

Acronyms and abbreviations

CI	Confidence interval
COVID-19	Coronavirus disease 2019
HR	Hazard ratio
PDC	Proportion of days covered
SD	Standard deviation
WHO	World Health Organization

List of figures

Figure 1. Compliance/adherence and persistence definitions. 16
Figure 2. Kaplan-Meier plot for acamprosate treatment persistence. 25
Figure 3. Kaplan-Meier plot for disulfiram treatment persistence. 26
Figure 4. Kaplan-Meier plot for nalmephen treatment persistence. 28
Figure 5. Kaplan-Meier plot for naltrexone treatment persistence. 29

List of tables

Table 1. Measures of medication adherence involving secondary database analysis and pill count. 15
Table 2. Baseline demographic characteristics of included participants per group. 23
Table 3. Univariable and multivariable hazard ratios analysis of COVID-19 impact on treatment persistence. 30
Table 4. Univariable hazard ratios analysis of COVID-19 impact on treatment persistence by gender and age group 31

Thesis outline

The present document describes the study that was conducted to estimate the impact of COVID-19 pandemic on alcohol dependence treatment.

This thesis consists of five sections: rationale, material and methods, results and discussion.

In the rationale section we present a structured review of alcohol consumption trend in Portugal, COVID-19 social impact and important concepts for the understanding of the present work.

The material and methods section comprises a detailed description of the methodologies adopted; it has the following subsections: study design and data source, data collection, outcome assessment, data analysis and ethics and data protection issues.

Results section presents participants characteristics, univariable and multivariable analysis by gender and age group.

The discussion section presents a critical view of the results, comparing it with results from other studies and identifies limitations of the study.

1. Rationale

According to the Global Burden of Disease Study, in 2016, alcohol dependence was the most prevalent of all substance use disorders, with a total of 100.4 million cases worldwide (1).

The last European Health Report stated that, in Portugal, in 2019, total alcohol consumption, per capita in adults was 12.1 L/year of pure alcohol (an increase of 1.6% compared to 2015), which is higher than the European average (9.5 L/year of pure alcohol) (2). According to the Ministry of Health, in 2018, 38.3% of Portuguese men and 11.8% of Portuguese women consumed alcohol on a daily basis, the highest values in Europe (3). This associates with an estimated prevalence of alcohol use disorders and alcohol dependence of 6.8% and 3.0%, respectively. Furthermore, alcohol was accountable for about 71% of liver cirrhosis cases, 37% of road traffic injuries, 7% of different types of cancer (4). Overall, in 2020, 2.544 people died from alcohol attributable diseases, which represented 2.1% of Portuguese mortality during that year (5).

A scoping review of primary care interventions of alcohol use disorder treatment that included pharmacotherapy (in some cases, alongside a non-pharmacological intervention), evaluated 25 different studies. This review has shown that pharmacological treatment for alcohol use disorders can reduce relapse, cravings, drinking frequency, and negative symptoms that occur immediately after alcohol withdrawal (6).

A real-world study conducted in Sweden aimed to estimate the effectiveness of alcohol dependence treatment with naltrexone in monotherapy and in combination with acamprosate or disulfiram. Study results have shown a lower risk of hospitalization when patients are treated with naltrexone compared to without treatment (1).

However, despite the positive outcomes of alcohol dependence treatment, a low rate of patients remain in treatment (7).

Medicine's adherence vs. persistence

Medicine's adherence and persistence are two different terms that describe medication-taking behaviours (8).

Medication adherence, also known as compliance, is defined as the degree to which a patient's behaviour complies with the prescribed medication regimen, including time, dose, and interval of medication intake (9).

Direct measures to estimate medicine's adherence include blood or urine tests for drug concentration and the direct observation of patients taking the medicine. Although direct measures are considered the most accurate, they are very expensive and require the involvement of health professionals to collect biological samples and perform the test. Secondary data collected during patients' appointments, hospitalizations and from medical prescriptions allow to estimate medication adherence through medication refill measures (Table 1). Refill measures assume that the prescription refill profile of a patient matches his medication taking behaviour (10,11). Compared to direct measures, secondary data provides a timely and easy access to information, allows to perform longitudinal analysis over long periods and to collect a bigger amount of data. On the other hand, data collected using this method may be complex and difficult to understand as investigators usually are not familiarized with it. One of the main disadvantages of secondary data collection is the absence of data quality control and the risk of not having the key variables to answer the research question (12).

Table 1. Measures of medication adherence involving secondary database analysis and pill count.

Measures	Equation
Medication Possession Ratio	Days' supply obtained/refill interval or fixed interval
Multiple Interval Measure of Medication Acquisition	Cumulative day supply obtained over a series of intervals/total days from the beginning to the end of the time period
Multiple Interval Measure of Medication Gaps	Cumulative days without any medication over a series of intervals/total days from the beginning to the end of the time period
Pill count	(Number of dosage units dispensed − number of dosage units remained)/(prescribed number of dosage unit per day × number of days between 2 visits)
Proportion of days covered (PDC)	(number of days in period "covered"/number of days in period) x 100%

Reference: Lam, 2015 (10) and MJH Life Sciences, 2015 (11).

Medication persistence is the act of continuing treatment for the prescribed time, being defined as "the duration of time from initiation to discontinuation of therapy" (8). Alternatively, it has been operationally defined based on the time between refills, the number of refills, prescription renewal with an allowance for a predetermined gap, and the proportion of patients continuing to refill prescriptions after a specified time. Figure 1 presents the differences between medication adherence and persistence (8).

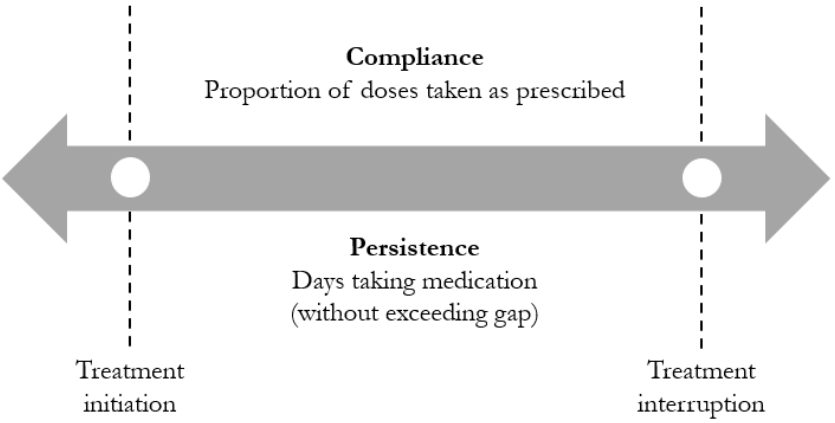


Figure 1. Compliance/adherence and persistence definitions.

Reference: Adapted from Cramer, 2008 (8).

Factors that modify adherence and persistence to medication

The common misconception that patients are completely responsible for taking their medication is deceptive and often reflects a misunderstanding of how various factors influence patients' behaviour and ability to follow up with their medication (13). Besides factors related to the patient (e.g. socioeconomic barrier, lack of health literacy), other variables can contribute to poor medication adherence and non-persistence, including physician-related (e.g. complex drug regimen prescription, ineffective communication) and health system-related factors (e.g. limited visit time and difficult access to health care) (13,14). Given that barriers to adherence and persistence are complex and varied, multifactor solutions are required to improve them (14). Investigating the cause of treatment non-adherence and non-persistence, enables the development of personalised interventions to improve medication taking behaviour of each individual (10).

COVID-19 and alcohol dependence

In early 2020, the World Health Organization (WHO) declared the Coronavirus disease 2019 (COVID-19) outbreak, a global pandemic (15). Across

the globe, millions of people got infected and about 6.6 million have died since then (16). Healthcare systems were at full capacity, so governments adopted preventive measures, such as social distance, lockdowns and masks, to avoid the rapid spread of the infection (17,18).

The COVID-19 pandemic imposed significant risks to marginalised people, particularly those with substance abuse disorders. Substance abuse is defined as the harmful or dangerous use of psychoactive substances such as alcohol and illegal drugs. One of the most significant effects of illicit drug use on society is the negative health consequences facing its members (19).

People with addictions, who are already underserved by the healthcare system, faced additional barriers to treatment, as hospitals and clinics focused on COVID-19 (20–22). Numerous studies have shown the negative consequences of the pandemic and lockdown on population mental health. According to several meta-analyses, the COVID-19 has aggravated mental health issues worldwide, particularly in terms of depression, anxiety, and sleep difficulties (23–26).

Regarding alcohol consumption patterns, several studies have been conducted on general population with different results (22,27–30). Psychosocial distress has been identified in all of these studies as a risk factor for relapse and increased alcohol use. However, it is equally important to examine how lockdowns and other restrictions affect patients who already have an alcohol use disorder when it comes to alcohol consumption. Considering this final point, Kim *et al.* (31) have found that lockdowns enhance alcohol consumption among those with alcohol use disorders and cause relapse in those who had previously abstained from alcohol. Furthermore, alcohol relapse increased alcohol-related emergencies including, withdrawal-related suicides, methanol toxicity and alcohol-related motor vehicle accidents (22,32).

Treatment persistence is an issue in many therapeutic areas, and it deserves particular concern among individuals with alcohol use disorder (33). Poor

treatment persistence during clinical trials has been identified as a barrier to estimate treatment efficacy *versus* placebo (34). In the real-world setting, some studies have assessed treatment persistence, revealing the negative health outcomes of treatment non-persistence, especially for those with alcohol dependence (1,6,7). To the best of our knowledge, no studies have assessed the impact of COVID-19 on alcohol dependence treatment persistence.

Objectives and research question

The primary objective is to estimate and compare persistence to alcohol dependence treatment before and after the start of COVID-19 pandemic through medicine sales data retrieved from Portuguese community pharmacies.

The secondary objectives are to describe the sociodemographic, and treatment patterns of patients; and to estimate treatment persistence by sex and age group.

This study research question is: Did the COVID-19 pandemic increased the risk of treatment non-persistence of patients with alcohol dependence?

2. Material and Methods

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE 2016) and the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Vandenbroucke et al. 2007).

Study design and data source

This is a retrospective cohort study of patients with a dispense of acamprosate, disulfiram, nalmephen or naltrexone in Portuguese community pharmacies. Medicine's sales data for the period between January of 2019 and March of 2022 were retrieved from the pharmacy's software database. This is an anonymised database, owned by the Portuguese National Association of Pharmacies, that includes more than 84% of the community pharmacies in Portugal. Data collected from this database include patients' age and sex, medical prescription details, such as physician specialty and medicines posology, medicines brand and/or international nonproprietary name, dosage, pack size, reimbursement regimen, among others. Data is collected at a patient-level.

We identified patients starting treatment with acamprosate, disulfiram, nalmephen or naltrexone and compared two different groups depending on the date when the treatment started:

- Group A: patients starting treatment with acamprosate, disulfiram, nalmephen or naltrexone between January 2019 and February 2020 (corresponding to one year before the start of the COVID-19 pandemic);

- Group B: patients starting treatment with acamprosate, disulfiram, nalmephen or naltrexone between March 2020 and March 2022 (corresponding to the period of the COVID-19 pandemic).

A patient taking multiple treatments may have different starting dates, meaning that he can be simultaneously included in groups A and B, if treated with different medicines.

Data collection

Dispensing data was collected using an electronic data transfer system and included information on the dosage, pack size and pharmaceutical form of the medication. In addition, for each patient, we retrieved information on their age and sex. For this study, data collection focused on prescription medicines indicated only for the treatment of alcoholism (acamprosate, disulfiram and nalmephen).

Outcome assessment

All analyses were separately performed by alcohol-treating medicine. All participants were followed up from their first medicine purchase: for 6 months, if treated with nalmephen or naltrexone; for 12 months, if treated with acamprosate or disulfiram. These are the recommended treatment duration for each medicine. Medicines first purchase was defined as the date without prior purchase of the same medicine in the last 90 days.

In this study, it was assumed that a patient was persistent to treatment if treatment interruptions occurred for less than 90 days. This means that, in order to be considered persistent to the treatment, a patient with a prescription that lasts 30 days would have to refill their medicine within 90 days from the last pill (otherwise, he would have been considered non-persistent and, therefore, censored).

Data analysis

Persistent patients were censored at the last day of the observation window (29 February 2020 for group A or 31 March 2022 for group B).

Discrete variables were summarized by absolute and relative frequencies. Numeric variables were summarized using means and standard deviations (SD) or medians and interquartile ranges.

Chi-square test was used to compare the distribution of participants' age and gender.

Kaplan-Meier survival analysis was used to estimate patients' persistence to treatment during follow-up. Hazard ratios were estimated using a Cox proportional hazard model. Univariable and multivariable logistic regression was used to analyze the impact of COVID-19 on patients' persistence to treatment (i.e., for comparing group A *versus* group B), with the regression models having been adjusted for age and sex. Univariable analysis by gender and age group was performed as sensitivity analysis. All applicable statistical tests were two-sided and performed at a 5% significance level. No imputation methods were applied on missing values.

Data analysis was performed using SAS Enterprise Guide v7.15.

Ethics and data protection issues

Database records anonymity is maintained in accordance with Portuguese laws and regulations, and in compliance with current personal data protection legislation, Regulation (EU) 2016/679 of the European Parliament and of the Council, of April 27, 2016, on Data Protection. Secondary data collected for this study had been previously anonymized, and for that reason a specific Institutional Review Board approval from an ethics committee was not needed (35,36).

3. Results

A total of 13.058 patients were included in this study. The majority were on treatment with acamprosate (n=4,974), followed by disulfiram (n= 4,682) and naltrexone (n=4,033). Only 683 patients were on treatment with nalmephen during the follow-up period. Patients' average age per group varied between 47.7 (SD = 13.0) and 53.5 (11.9) years. In all medicines, the majority of the patients on treatment were men, with the percentage of males per group ranging from 54.6% in group B of naltrexone to 79.1% in group A of acamprosate. A significant difference was found in participants sex that were on treatment with acamprosate, disulfiram and naltrexone. The age group analysis showed that there are more people on treatment between 45-54 years. A significant difference was found in the age group of patients treated with acamprosate (Table 2).

Table 2. Baseline demographic characteristics of included participants per group.

Demographic characteristics	Acamprosate (n=4,974)			Disulfiram (n=4,682)			Nalmephen (n=683)			Naltrexone (n=4,033)		
	Group A (n=2,105)	Group B (n=2,869)	P-value	Group A (n=2,156)	Group B (n=2,526)	P-value	Group A (n=318)	Group B (n=365)	P-value	Group A (n=1,676)	Group B (n=2,357)	P-value
Gender, n (%)												
Male	1,584 (79.1)	2,024 (73.5)	<0.001	1,522 (74.6)	1,703 (71.3)	0.013	215 (70.0)	241 (67.7)	0.518	1,067 (65.9)	1,240 (54.6)	<0.001
Age, years												
Mean (SD)	53.5 (11.9)	51.4 (11.8)		51.0 (11.0)	50.5 (11.4)		52.4 (12.6)	50.4 (12.5)		48.6 (12.8)	47.7 (13.0)	
Age groups, n (%)												
18-24	17 (0.8)	31 (1.1)		20 (0.9)	32 (1.3)		3 (0.9)	7 (1.9)		42 (2.5)	69 (3.0)	
25-34	96 (4.6)	196 (6.8)		112 (5.3)	152 (6.1)		23 (7.3)	31 (8.5)		191 (11.5)	290 (12.5)	
35-44	388 (18.5)	570 (19.9)		465 (21.8)	586 (23.4)		60 (18.9)	74 (20.3)		405 (24.4)	618 (26.7)	
45-54	613 (29.3)	950 (33.2)	<0.001	761 (35.7)	854 (34.1)	0.387	90 (28.4)	117 (32.1)	0.566	512 (30.8)	659 (28.5)	0.331
55-64	603 (28.8)	723 (25.3)		529 (24.8)	594 (23.7)		89 (28.1)	89 (24.4)		322 (19.4)	441 (19.0)	
65-74	292 (13.9)	312 (10.9)		204 (9.6)	230 (9.2)		38 (12.0)	36 (9.9)		149 (9.0)	182 (7.9)	
≥75	86 (4.1)	81 (2.8)		39 (1.8)	56 (2.2)		14 (4.4)	11 (3.0)		42 (2.5)	57 (2.5)	

For patients treated with acamprosate, treatment non-persistence rate at 12 months was 93.2% and 91.4% for groups A and B, respectively. Persistence rate at 90 days was 33.2% in group A and 29.4% in group B; and at 180 days was 15.0% in group A and 15.6% in group B. Median duration of treatment was 43.0 days (95% CI: 40.0 to 50.0) in group A and 38.0 days (95% CI: 33.0 to 40.0) in group B.

The Kaplan Meier plot for treatment persistence with this medicine has revealed that patients' persistence in each group crosses each other, approximately 150 days after treatment initiation. Schoenfeld residuals test have shown that distribution is not proportional and identified an inflection point at 90 days. To comply with the assumptions of the Cox model assumptions that survival curves must have proportional hazard functions over time and that each covariate's relationship to the log hazard is linear (37), we have segmented the acamprosate persistence analysis into two:

- Persistence analysis in the first 90 days of treatment;
- Persistence analysis after 90 days of treatment.

The univariable Cox regression model for acamprosate treatment in the first 90 days estimated an HR of 1.10 (95% CI: 1.03 to 1.18, p=0.007), meaning that the COVID-19 period was associated with an increased risk of treatment non-persistence with acamprosate. Similar results were obtained with a multivariable model adjusted for age and sex with an HR of 1.08 (95% CI: 1.00 to 1.16, p=0.044) (Table 3). We observed that the COVID-19 period did not impact women persistence to acamprosate (HR: 1.11; 95% CI: 0.95 to 1.28; p=0.193). However, for men, we observed an increased risk of non-persistence to this treatment (HR: 1.11; 95% CI: 1.03 to 1.21; p= 0.011). Regarding age group sensitivity analysis, there were no differences of treatment persistence in any group (Table 4).

When analyzing, patients' persistence after 90 days of treatment, the univariable Cox regression model has estimated an HR of 0.76 (95% CI: 0.66 to

0.86, p<0.001), meaning treatment initiation during the COVID-19 pandemic was associated with reduced risk of non-persistence to acamprosate. Similar results were obtained in multivariable models (HR: 0.74; 95% CI: 0.65 to 0.85, p<0.001) (Table 3), and both when performing separate analyses for men (HR: 0.79; 95% CI: 0.67 to 0.92; p=0.002) and women (HR: 0.71; 95% CI: 0.54 to 0.95; p=0.019). In terms of univariable analysis by age groups, the pandemic period has significantly reduced the risk of acamprosate treatment non-persistence of patients aged 35-44, 45-54 and 65-74 years. The remaining groups have shown a similar risk of treatment non-persistence (Table 4).

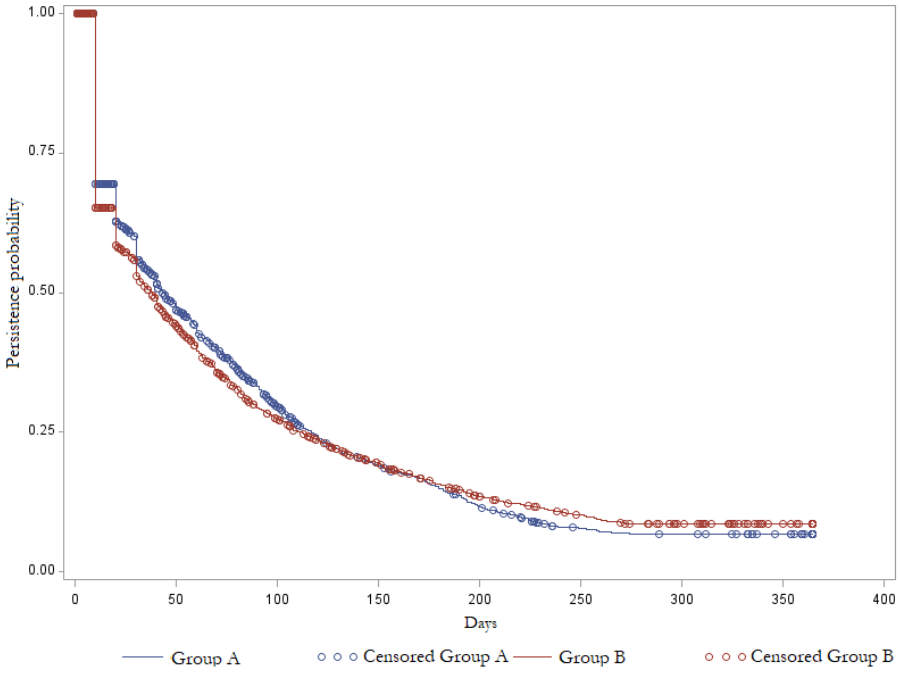


Figure 2. Kaplan-Meier plot for acamprosate treatment persistence.

Regarding alcohol dependence treatment with disulfiram, at 12 months, 67.7% and 70.8% patients were non-persistent to treatment in groups A and B, respectively. Persistence rate at 90 days was 97.6% in group A and 93.9% in

group B; and at 180 days it was 46.2% in group A and 42.6% in group B. Median duration of treatment was of 120.0 days for both groups. Figure 3 shows the Kaplan-Meier plot for persistence with disulfiram. In univariable Cox regression models, we observed that the COVID-19 period was associated with an increased risk of treatment non-persistence with disulfiram (HR: 1.11; 95% CI: 1.02 to 1.20, p=0.013). Multivariable regression models showed similar results (HR: 1.10; 95% CI: 1.01 to 1.19, p=0.032) (Table 3). Univariable analysis by gender have found that starting treatment during the COVID-19 period did not affect women persistence to disulfiram (HR: 1.01; 95% CI: 0.86 to 1.17; p=0.950) but affected that of men (HR: 1.14; 95% CI: 1.03 to 1.25; p= 0.011). The COVID-19 period has also significantly affected persistence to disulfiram in patients aged 45-54 years (HR: 1.21; 95% CI: 1.05 to 1.40; p=0.008) but not of the remaining age groups (Table 4).

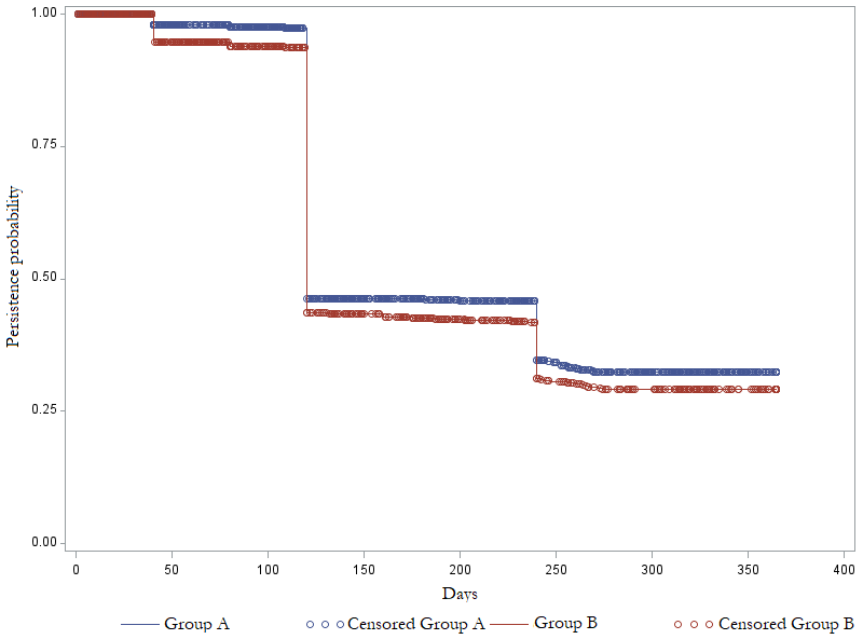


Figure 3. Kaplan-Meier plot for disulfiram treatment persistence.

Considering treatment with nalmephen, at 6 months, 68.3% of the patients in group A and 84.4% of the patients in group B were non-persistent to treatment. Persistence rate at 45 days was of 43.8% in group A and 32.5% in group B; and at 90 days it was of 31.7% in group A and 15.6% in group B. The median duration of treatment was 28.0 days for both groups. Patients' persistence to nalmephen is illustrated in Figure 4. In univariable Cox regression models, the COVID-19 was found to be associated with an increased risk of treatment non-persistence with nalmephen (HR: 1.44; 95% CI: 1.21 to 1.70, $p<0.001$). Multivariable Cox regression models showed similar results (HR: 1.40; 95% CI: 1.18 to 1.66, $p<0.001$) (Table 3). The pandemic period was significantly associated with an increased risk of nalmephen treatment non-persistence in both men (HR: 1.42; 95% CI: 1.15 to 1.74; $p=0.001$) and women (HR: 1.43; 95% CI: 1.06 to 1.95; $p=0.021$). Regarding age groups, the pandemic period was associated with a significantly increased risk of nalmephen treatment non-persistence in patients aged 25-34, 35-44 and 65-74 years (Table 4).

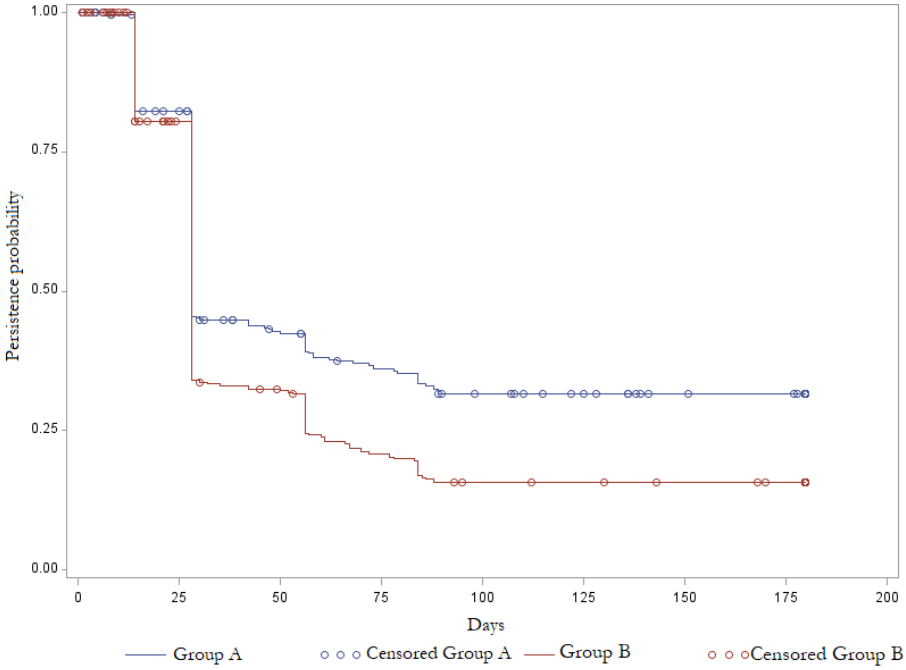


Figure 4. Kaplan-Meier plot for nalmephen treatment persistence.

Considering patients on treatment with naltrexone, 56.3% and 63.6% of patients from group A and B, respectively, were non-persistent to treatment at 6 months. Persistence at 45 days was of 82.1% in group A and 79.6% in group B; and at 90 days was of 43.7% in group A and 36.4% in group B. The median duration of treatment was of 60.0 days for both groups. Figure 5 shows patients' persistence to naltrexone. Univariable Cox regression models estimated an HR of 1.23 (95% CI: 1.14 to 1.32, $p<0.001$), indicating that the pandemic period was associated with an increased risk of naltrexone treatment non-persistence. Multivariable Cox models revealed a similar result with an HR of 1.20 (95% CI: 1.11 to 1.30, $p<0.001$) (Table 3). The COVID-19 period did not impact women's persistence to naltrexone (HR: 1.10; 95% CI: 0.97 to 1.24; $p=0.130$) but was associated with a significant impact in men (HR: 1.29; 95% CI: 1.17 to 1.42;

p<0.001). Across age groups, the COVID-19 period was significantly associated with an increased risk of naltrexone non-persistence in patients 35-44, 45-54, and 55-64 years of age (Table 4).

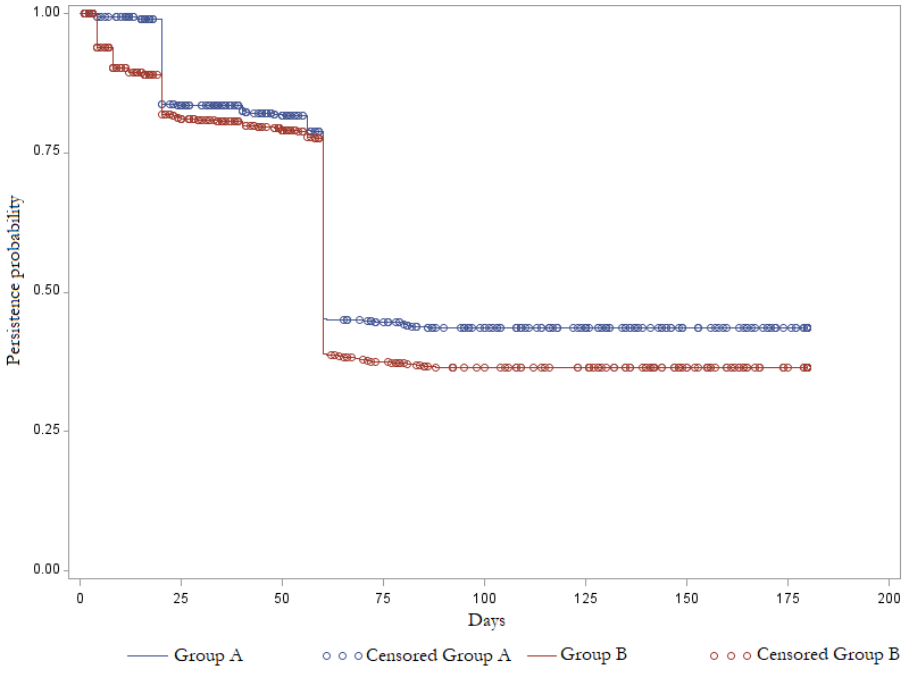


Figure 5. Kaplan-Meier plot for naltrexone treatment persistence.

Table 3. Univariable and multivariable hazard ratios analysis of COVID-19 impact on treatment persistence.

Medicine	Univariable HR (95% CI)	P-value	Multivariable HR* (95% CI)	P-value
Acamprosate ≤ 90 days	1.10 (1.03 to 1.18)	0.007	1.08 (1.00 to 1.16)	0.044
Acamprosate > 90 days	0.76 (0.66 to 0.86)	<0.001	0.74 (0.65 to 0.85)	<0.001
Disulfiram	1.11 (1.02 to 1.20)	0.013	1.10 (1.01 to 1.19)	0.032
Nalmephen	1.44 (1.21 to 1.70)	<0.001	1.40 (1.18 to 1.66)	0.001
Naltrexone	1.23 (1.14 to 1.32)	<0.001	1.20 (1.11 to 1.30)	<0.001

HR>1 favours Group A; *Adjusted for age and sex

Table 4. Univariable hazard ratios analysis of COVID-19 impact on treatment persistence by gender and age group.

Factor	Acamprosate < 90 days		Acamprosate ≥ 90 days		Disulfiram		Nalmephen		Naltrexone	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Gender										
Female	1.11 (0.95 to 1.28)	0.193	0.71 (0.54 to 0.95)	0.019	1.01 (0.86 to 1.17)	0.950	1.43 (1.06 to 1.95)	0.021	1.10 (0.97 to 1.24)	0.130
Male	1.11 (1.03 to 1.21)	0.011	0.79 (0.67 to 0.92)	0.002	1.14 (1.03 to 1.25)	0.011	1.42 (1.15 to 1.74)	0.001	1.29 (1.17 to 1.42)	<0.001
Age group										
18-24	0.60 (0.30 to 1.20)	0.150	0.43 (0.07 to 2.61)	0.360	0.71 (0.36 to 1.40)	0.319	3.25 (0.39 to 26.91)	0.275	1.07 (0.69 to 1.66)	0.757
25-34	0.84 (0.64 to 1.11)	0.226	0.98 (0.42 to 2.25)	0.954	1.08 (0.77 to 1.51)	0.670	1.91 (1.03 to 3.55)	0.040	1.19 (0.96 to 1.47)	0.108
35-44	1.08 (0.93 to 1.26)	0.316	0.69 (0.50 to 0.96)	0.026	1.05 (0.88 to 1.24)	0.605	1.50 (1.02 to 2.20)	0.040	1.20 (1.04 to 1.39)	0.014
45-54	1.08 (0.96 to 1.23)	0.211	0.70 (0.55 to 0.90)	0.005	1.21 (1.05 to 1.40)	0.008	1.16 (0.86 to 1.56)	0.330	1.19 (1.03 to 1.36)	0.015
55-64	1.13 (0.99 to 1.30)	0.081	0.90 (0.70 to 1.14)	0.382	1.04 (0.88 to 1.22)	0.657	1.36 (0.97 to 1.90)	0.071	1.38 (1.16 to 1.65)	<0.001
65-74	1.08 (0.88 to 1.34)	0.457	0.50 (0.35 to 0.70)	<0.001	1.12 (0.85 to 1.46)	0.426	2.08 (1.21 to 3.59)	0.008	1.24 (0.97 to 1.60)	0.092
≥75	1.07 (0.73 to 1.56)	0.746	0.70 (0.37 to 1.34)	0.283	1.05 (0.63 to 1.74)	0.865	1.09 (0.44 to 2.68)	0.858	1.32 (0.83 to 2.10)	0.240

4. Discussion

This was a retrospective cohort study of patients on alcohol dependence treatment that were followed in Portuguese community pharmacies between January of 2019 and March of 2022.

This study found that patients who started their alcohol dependence treatment during the COVID-19 displayed an increased risk of treatment non-persistence with disulfiram, nalmephen and naltrexone. Besides alcohol dependence treatment, naltrexone is also indicated in the treatment of opioid dependence. However, it is only used under exceptional circumstances, as evidence does not support the use of oral naltrexone as an effective treatment for opioid use disorder relapse prevention (41). For that reason, it was assumed that naltrexone sales data would concern patients with alcohol dependence.

Regarding acamprosate, in the first 90 days of treatment, the pandemic was associated with an increased risk of non-persistence to this medicine, but the opposite effect was observed for the subsequent period. Gender-related differences were also identified - males have shown an increased risk of treatment non-persistence associated with COVID-19 for any of these medicines. For females, only patients treated with nalmephen have shown a significant increased risk of treatment non-persistence associated with the pandemic. Regarding age, less consistent results were observed.

These results may be due to different factors, including the difficulty in accessing healthcare due to the focus on the pandemic, confinement measures, changes in individual and collective behaviour in an emergency situation or even low income (38). Several studies have assessed gender differences in attitudes and behaviours during the pandemic, showing that women were more likely to agree and follow through with restraint measures, once they perceived the COVID-19 pandemic as a very serious health issue (39,40). This is probably reflected in their

attitude towards treatment and may explain the higher risk of treatment non-persistence among men than in women.

Thompson *et al.* have conducted a cohort study to evaluate treatment of alcohol dependence 12 months after diagnosis in the United Kingdom between 1990 and 2013. In this study, treatment persistence was estimated using a similar method of Kaplan-Meier survival analysis. Persistence analysis showed that many patients did not receive a second prescription. Treatment persistence at 6 months was 28% for acamprosate and 33% for disulfiram; and the median duration of therapy was 2.10 months and 3.13 months for acamprosate and disulfiram, respectively. They also have found that being male and older significantly reduced the chance of receiving treatment for alcohol dependence (42). We have found a similar trend, with a lower treatment persistence rate at 6 months for patients treated with acamprosate (15,0% in group A and 15,6% in group B) *vs.* disulfiram (46,2% in group A and 42,6% in group A). Regarding the duration of therapy, our study results revealed that patients treated with acamprosate, interrupted treatment in an earlier phase, as the median duration of therapy was 1.43 months. Patients treated with disulfiram revealed a better compliance to therapy, as their median duration of treatment was 4,0 months.

Across the world, different studies have assessed the impact of the pandemic on patient adherence to treatment. A single-centre study in the United States of America, aimed to estimate the impact of the pandemic on the adherence to oral endocrine therapy used to prevent or treat breast cancer. This retrospective study has found that patients' adherence during the pandemic was significantly lower compared to before the pandemic (44% *vs.* 57%) (43). Another study conducted in Japan aimed to evaluate denosumab therapy adherence before and during COVID-19. This medicine is a monoclonal antibody for osteoporosis treatment administered subcutaneously every 6 months. Study results showed similar persistence rates in the pandemic and non-pandemic group. This could be due to the rare frequency of administration of this drug (44).

It is known that in the coming decades, the risk of extreme epidemics like COVID-19 will increase by up to three times (45). In this sense, the WHO has recently identified the main factors that will define the next epidemic (46). In addition to the type and transmissibility of the pathogen, one of the issues that deserves special attention is the response and capacity of the health care systems. In fact, a significant part of the population experienced challenges in accessing health care services during COVID-19 pandemic, especially those with chronic diseases (38,47,48).

Some limitations to this work should be noted. Methodological limitations and generating bias were inherent to the observational design adopted in this study. One was the potential bias introduced by missing data, which is a common limitation of observational studies. Medicines refill does not ensure that patients take their prescription as recommended. Furthermore, uncontrolled confounding may exist given some characteristics that can influence adherence/persistence, such as educational level, income, family support, and other comorbidities which were not adjusted in this study analysis.

Other relevant aspects might have affected this study results. Patients who have started treatment before the pandemic and should continue during that period were excluded from the analysis. Consequently, for these cases, we did not estimate how it has affected patients' persistence to treatment. The regional distribution of study participants, before and after the pandemic, was not analyzed. Due to the lockdowns, people have moved to rural areas and therefore they may have modified their behaviour and treatment patterns. The number of patients who have started alcohol dependence treatment in the pre-pandemic group (1 year of data collection) was very similar to the number of patients who have started therapy in the pandemic period (2 years of data collection). This suggests that during the COVID-19 period, the reduced availability of non-COVID healthcare resulted in an inferior number of patients being treated for alcohol dependence. It should be assessed if patients with alcohol use disorders

that have started treatment during the pandemic reflect worst cases, and if for that reason, their persistence to treatment is different from a patient with a less severe disorder.

This study suggests that COVID-19 negatively impacted patients' persistence to alcohol dependence treatment. A similar trend is expected in other therapeutical areas.

As countries worldwide struggled to contain COVID-19 pandemic, in the future, healthcare services should undergo a significant rearrangement in order to effectively fulfil the needs of patients with substance use disorders and other chronic diseases. The association of COVID-19 with treatment persistence suggests that patients need frequent follow-up medical visits to closely monitor their treatment compliance, and consequently, to improve their health and prevent additional costs to society and the health system. Further research is needed to evaluate the adequate model of services provided, such as telemedicine or follow-up with the pharmacist.

5. References

1. Heikkinen M, Taipale H, Tanskanen A, Mittendorfer-Rutz E, Lähteenvuo M, Tiihonen J. Real-world effectiveness of pharmacological treatments of alcohol use disorders in a Swedish nation-wide cohort of 125 556 patients. Addiction. 2021;116(8):1990–8.
2. World Health Organization. The European Health Report 2021. Vol. 23, Quaderni ACP. 2021.
3. Ministério da Saúde. Retrato da Saúde 2018. 2018;
4. Hammer JH, Parent MC, Spiker DA, World Health Organization. Global status report on alcohol and health 2018 [Internet]. Vol. 65, Global status report on alcohol. 2018. 74–85 p. Available from: https://www.who.int/publications/i/item/9789241565639
5. Serviço de Intervenção nos Comportamentos Aditivos e nas Dependências. Relatório Anual 2021 - A Situação do País em Matéria de Álcool [Internet]. 2022. Available from: https://www.sicad.pt/PT/Publicacoes/Paginas/detalhe.aspx?itemId=180&lista=SICAD_PUBLICACOES&bkUrl=BK/Publicacoes/
6. Hyland C, McDowell M, Bain P, Huskamp H, Busch A. Integration of pharmacotherapy for alcohol use disorder treatment in primary care settings: A scoping review. J Subst Abus Treat [Internet]. 2023;144(108919). Available from: https://pubmed.ncbi.nlm.nih.gov/36332528/
7. Tolomeo S, Baldacchino A. Adherence to prescribed acamprosate in alcohol dependence and 1-year morbidities and mortality: Utilizing a data linkage methodology. J Clin Med. 2021;10(10):1–10.
8. Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA, et al. Medication compliance and persistence: Terminology and definitions. Value Heal [Internet]. 2008;11(1):44–7. Available from: http://dx.doi.org/10.1111/j.1524-4733.2007.00213.x
9. Gast A, Mathes T. Medication adherence influencing factors — an (updated) overview of systematic reviews. 2019;1–17.
10. Lam WY, Fresco P. Medication Adherence Measures : An Overview. 2015;2015.
11. MJH Life Sciences. Do You Know the Difference Between These Adherence Measures? [Internet]. 2015. Available from: https://www.pharmacytimes.com/view/do-you-know-the-difference-between-these-adherence-measures
12. Bell E, Bryman A, Harley B. Planning a research project and developing research questions. In: Business Research Methods (5th edn) Oxford,

Oxford University Press. 2019. p. 80–5.
13. World Health Organization. Adherence to long-term therapies: evidence for action. 2003;
14. Brown MT, Bussell JK. Medication adherence: WHO cares? Mayo Clin Proc [Internet]. 2011 [cited 2023 Jan 28];86(4):304–14. Available from: https://pubmed.ncbi.nlm.nih.gov/21389250/
15. World Health Organization. Director-General's opening remarks at the media briefing on-COVID-19. [Internet]. 2020 [cited 2022 Dec 8]. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020
16. World Health Organization. WHO Coronavirus (COVID-19) Dashboard [Internet]. 2022 [cited 2022 Dec 8]. Available from: https://covid19.who.int/
17. Romano S, Galante H, Figueira D, Mendes Z, Rodrigues AT. Time-trend analysis of medicine sales and shortages during COVID-19 outbreak: Data from community pharmacies. 2020;
18. Bottemanne H, Friston KJ. An active inference account of protective behaviours during the COVID-19 pandemic. Cogn Affect Behav Neurosci. 2021;21(6):1117–29.
19. Substance Abuse | WHO | Regional Office for Africa [Internet]. [cited 2022 Nov 19]. Available from: https://www.afro.who.int/health-topics/substance-abuse
20. Horner G, Daddona J, Burke DJ, Cullinane J, Skeer M, Wurcel AG. "You're kind of at war with yourself as a nurse": Perspectives of inpatient nurses on treating people who present with a comorbid opioid use disorder. PLoS One. 2019;14(10):1–16.
21. Samuels EA, Clark SA, Wunsch C, Jordison Keeler LA, Reddy N, Vanjani R, et al. Innovation During COVID-19: Improving Addiction Treatment Access. J Addict Med [Internet]. 2020 Jul 1 [cited 2022 Dec 9];14(4). Available from: https://pubmed.ncbi.nlm.nih.gov/32404652/
22. Murthy P, Narasimha VL. Effects of the COVID-19 pandemic and lockdown on alcohol use disorders and complications. Curr Opin Psychiatry [Internet]. 2021 Apr 2 [cited 2022 Dec 9];34(4):376–85. Available from: https://pubmed.ncbi.nlm.nih.gov/34016817/
23. Salari N, Hosseinian-Far A, Jalali R, Vaisi-Raygani A, Rasoulpoor S, Mohammadi M, et al. Prevalence of stress, anxiety, depression among the general population during the COVID-19 pandemic: A systematic review and meta-analysis. Global Health. 2020;16(1):1–11.
24. Luo M, Guo L, Yu M, Wang H. The psychological and mental impact of coronavirus disease 2019 (COVID-19) on medical staff and general public – A systematic review and meta-analysis. Psychiatry Res [Internet]. 2020;291:113190. Available from:

https://doi.org/10.1016/j.psychres.2020.113190
25. Nochaiwong S, Ruengorn C, Awiphan R, Ruanta Y, Boonchieng W, Nanta S, et al. Mental health circumstances among health care workers and general public under the pandemic situation of COVID-19 (HOME-COVID-19). Med (United States). 2020;99(26):E20751.
26. Wu T, Jia X, Shi H, Niu J, Yin X, Xie J, et al. Prevalence of mental health problems during the COVID-19 pandemic: A systematic review and meta-analysis. J Affect Disord. 2021;281(January):91–8.
27. Mallet J, Dubertret C, Le Y. Addictions in the COVID-19 era : Current evidence , future perspectives a comprehensive review. Prog Neuro-Psychopharmacology Biol Psychiatry. 2021;106.
28. Ramalho R. Alcohol consumption and alcohol-related problems during the COVID-19 pandemic: a narrative review. Aust Psychiatry. 2020;28(5):524–6.
29. Villanueva-Blasco VJ, Villanueva Silvestre V, Isorna M, Motos P, Blay P, Vázquez-Martínez A. Changes in alcohol consumption pattern based on gender during covid-19 confinement in spain. Int J Environ Res Public Health. 2021;18(15).
30. Althobaiti YS, Alzahrani MA, Alsharif NA, Alrobaie NS, Alsaab HO, Uddin MN. The possible relationship between the abuse of tobacco, opioid, or alcohol with covid-19. Healthc. 2021;9(1):1–12.
31. Kim J, Majid A, Judge R, Crook P, Nathwani R, Selvapatt N, et al. Effect of COVID-19 lockdown on alcohol consumption in patients with pre-existing alcohol use disorder. Lancet Gastroenterol Hepatol. 2020;5(10):886–7.
32. Roberts A, Rogers J, Mason R, Niroshan A, Hogue T, Adam G, et al. Alcohol and other substance use during the COVID-19 pandemic : A systematic review. Drug Alcohol Depend [Internet]. 2021;229(PA):109150. Available from: https://doi.org/10.1016/j.drugalcdep.2021.109150
33. Kranzler H, Stephenson J, Montejano L, Wang S, Gastfriend D. Persistence with Oral Naltrexone for Alcohol Treatment: Implications for Healthcare Utilization. Addiction. 2008;103(11).
34. Baros AM, Latham PK, Moak DH, Voronin K, Anton RF. What role does measuring medication compliance play in evaluating the efficacy of naltrexone? Alcohol Clin Exp Res. 2007;31(4):596–603.
35. Murteira R, Guerreiro J, Cary M, Teixeira Rodrigues A. POSC372 The Phollow Cohort: Real-world therapeutic adherence to oral anticoagulants in Portugal. Value Heal [Internet]. 2022;25(1). Available from: https://www.valueinhealthjournal.com/article/S1098-3015(21)02992-2/fulltext
36. Murteira R, Guerreiro J, Cary M, Teixeira Rodrigues A. POSA372 The Phollow Cohort: Quality of life of patients using antidiabetic or oral

anticoagulants agents in Portugal. 2022;25(1). Available from: https://www.valueinhealthjournal.com/article/S1098-3015(21)02878-3/fulltext
37. Hashim D, Weiderpass E. Cancer Survival and Survivorship. Encycl Cancer. 2019 Jan 1;250–9.
38. Folayan MO, Abeldaño Zuñiga RA, Virtanen JI, Ezechi OC, Yousaf MA, Al-Tammemi AB, et al. A multi-country survey on access to healthcare and treatment services among individuals with critical medical care needs during the first wave of the pandemic. BMC Public Health [Internet]. 2023;23(1):1–10. Available from: https://doi.org/10.1186/s12889-023-15007-0
39. Galasso V, Pons V, Profeta P, Becher M, Brouard S, Foucault M. Gender differences in COVID-19 attitudes and behavior: Panel evidence from eight countries. Proc Natl Acad Sci U S A. 2020;117(44):27285–91.
40. Reisch T, Heiler G, Hurt J, Klimek P, Hanbury A, Thurner S. Behavioral gender differences are reinforced during the COVID-19 crisis. Sci Rep [Internet]. 2021;11(1):1–12. Available from: https://doi.org/10.1038/s41598-021-97394-1
41. American Society of Addiction Medicine. The ASAM National Practice Guideline for the Treatment of Opioid Use Disorder: 2020 Focused Update. 2020;
42. Thompson A, Ashcroft DM, Owens L, Van Staa TP, Pirmohamed M. Drug therapy for alcohol dependence in primary care in the UK: A Clinical Practice Research Datalink study. PLoS One. 2017;12(3):1–14.
43. Rahimi S, Ononogbu O, Mohan A, Moussa D, Abughosh S, Trivedi M V. Adherence to oral endocrine therapy in racial/ethnic minority patients with low socioeconomic status before and during the COVID-19 pandemic. Int J Clin Pharm [Internet]. 2023; Available from: https://doi.org/10.1007/s11096-023-01609-6
44. Kobayashi K, Sato K, Ando T, Ando K, Imura S. Impact of the COVID-19 Pandemic on Adherence to Denosumab Therapy : A Single Center Study. 2023;
45. Marani M, Katul GG, Pan WK, Parolari AJ. Intensity and frequency of extreme novel epidemics. Proc Natl Acad Sci U S A. 2021;118(35):0–3.
46. World Health Organization. Imagining the future of pandemics and epidemics: a 2022 perspective. 2022;
47. Mularczyk-Tomczewska P, Zarnowski A, Gujski M, Jankowski M, Bojar I, Wdowiak A, et al. Barriers to accessing health services during the COVID-19 pandemic in Poland: A nationwide cross-sectional survey among 109,928 adults in Poland. Front Public Heal. 2022;10.
48. Khattar J, Anderson LN, De Rubeis V, de Groh M, Jiang Y, Jones A, et al. Unmet health care needs during the COVID-19 pandemic among

adults: a prospective cohort study in the Canadian Longitudinal Study on Aging. C open. 2023;11(1):E140–51.