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Tobacco consumption during the COVID-19 pandemic and pharmacokinetic interaction involving cytochrome P-450 with psychoactive drugs: an integrative review

Consumo de tabaco durante a pandemia de COVID-19 e interação farmacocinética envolvendo citocromo P-450 com fármacos psicoativos: uma revisão integrativa

Consumo de tabaco durante la pandemia de COVID-19 e interacción farmacocinética del citocromo P-450 con las drogas psicoactivas: una revisión integradora

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Abstract
This integrative review examines tobacco use related to mental disorders in COVID-19 pandemic and potential interactions involving cytochrome P-450 between tobacco and psychotropic drugs. The five steps of the integrative review development process were considered, namely: elaboration of the guiding question, literature search or sampling, evaluation of data, data analysis, interpretation and presentation of results. A literature search was performed in the Medline and Bireme databases, without language restrictions up to May 2021. Forty-seven articles were found with information on COVID-19, tobacco use and psychiatric illness. Articles were also sought that addressed interactions between major classes of psychotropic drugs and tobacco associated with CYP450 isoforms and genetic polymorphism. Thirty-seven articles were found for interaction among tobacco, cytochrome P450 and antidepressants; 7 including polymorphism; 19 articles involving interaction of tobacco, cytochrome P450 and antipsychotics; 4 including polymorphism; 3 articles describing interaction of tobacco, cytochrome P450 and anxiolytics; 1 including polymorphism; 2 articles regarding interaction of tobacco, cytochrome P450 and mood stabilizers; and 1 including polymorphism. These findings reinforce the importance of recognizing the role of tobacco associated with drug use in mental disorders; indicating the need for monitoring to prevent worsening clinical conditions.
Keywords: Tobacco; COVID-19; Psychotropic drugs; Drug interactions.

Resumo
Esta revisão integrativa investiga o consumo de tabaco relacionado com enfermidades mentais na pandemia de COVID-19 e potenciais interações envolvendo o citocromo P-450, tabaco e os fármacos psicotrópicos. Foram consideradas as cinco etapas do processo de desenvolvimento da revisão integrativa, a saber: elaboração da pergunta orientadora, pesquisa bibliográfica ou amostragem, avaliação dos dados, análise dos dados, interpretação e apresentação dos resultados. Foi realizada uma pesquisa bibliográfica nas bases de dados Medline e Bireme, sem restrições linguísticas até maio de 2021. Foram encontrados quarenta e sete artigos com informações sobre a COVID-19, o uso do tabaco e doenças psiquiátricas. Foram também procurados artigos que abordassem interações entre as principais classes de fármacos psicotrópicos e tabaco associados às isoformas de CYP450 e polimorfismo genético. Foram encontrados 37 artigos para interação entre tabaco, citocromo P450 e antidepressivos; 7 incluindo polimorfismo; 19 artigos envolvendo interação de tabaco, citocromo P450 e antipsicóticos; 4 incluindo polimorfismo; 3 artigos descrevendo interação de tabaco, citocromo P450 e ansiolíticos; 1 incluindo polimorfismo; 2 artigos envolvendo interação de tabaco, citocromo

P450 e estabilizadores de humor; e 1 incluindo polimorfismo. Esses achados reforçam a importância de reconhecer o papel do tabaco associado ao uso de fármacos para enfermidades mentais; indicando a necessidade de monitorização para prevenir o agravamento das condições clínicas.
Palavras-chave: Tabaco; COVID-19; Fármacos psicotrópicos; Interações medicamentosas.

Resumen
Esta revisión integradora examina el consumo de tabaco relacionado con los trastornos mentales en la pandemia de COVID-19 y las posibles interacciones que implican al citocromo P-450 entre el tabaco y los fármacos psicotrópicos. Se consideraron los cinco pasos del proceso de desarrollo de la revisión integradora, a saber: elaboración de la pregunta guía, búsqueda de literatura o muestreo, evaluación de datos, análisis de los datos, interpretación y presentación de los resultados. Se realizó una búsqueda bibliográfica en las bases de datos Medline y Bireme, sin restricciones de idioma hasta mayo de 2021. Se encontraron 47 artículos con información sobre la COVID-19, el consumo de tabaco y las enfermedades psiquiátricas. También se buscaron artículos que abordaran las interacciones entre las principales clases de fármacos psicotrópicos y el tabaco asociadas a las isoformas del CYP450 y al polimorfismo genético. Se encontraron 37 artículos sobre la interacción entre el tabaco, el citocromo P450 y los antidepresivos; 7 incluían el polimorfismo; 19 artículos sobre la interacción del tabaco, el citocromo P450 y los antipsicóticos; 4 incluían el polimorfismo; 3 artículos describían la interacción del tabaco, el citocromo P450 y los ansiolíticos; 1 incluía el polimorfismo; 2 artículos sobre la interacción del tabaco, el citocromo P450 y los estabilizadores del estado de ánimo; y 1 incluía el polimorfismo. Estos hallazgos refuerzan la importancia de reconocer el papel del tabaco asociado al consumo de fármacos en los trastornos mentales; indicando la necesidad de control para prevenir el empeoramiento de las condiciones clínicas.
Palabras clave: Tabaco; COVID-19; Fármacos psicotrópicos; Interacciones farmacológicas.

1. Introduction

The period of the COVID-19 pandemic has been marked by an increase in emotional issues such as depression, bipolar disorder, anxiety, and schizophrenia. Therefore, an increase in the consumption of psychotropic drugs and tobacco can be considered. In this sense, the possibility exists of drug-smoking interaction, with reduction or increase of the pharmacological effects. Here, we presented the tobacco use related to mental disorders in COVID-19 pandemic and potential interactions involving cytochrome P-450 between tobacco and psychotropic drugs. In this integrative review, we reinforce the importance of recognizing the role of tobacco associated with drug use in mental disorders and the need for monitoring to prevent worsening clinical conditions.

The abuse of psychoactive substances with therapeutic properties (Perelló et al., 2021) is an additional problem to the abuse of substances without therapeutic properties. The most common examples are tobacco and alcohol. Both provide pleasant (hedonic) effects but often lead to addiction (Augustin et al., 2018).

The higher prevalence of smoking among people with psychiatric disorders than those in the general population has been reported by several studies. Tobacco use is an important risk factor for morbidity and mortality worldwide (Reitsma et al., 2017; Rehman et al.; 2021; Laviolette, 2021). In this context, people with psychiatric disorders who have never smoked have a significantly better quality of life and are less susceptible to depressive symptoms (King et al. 2018; Nur et al., 2017; Becoña et al., 2013).

Smoking is a relevant factor to consider regarding drug therapy. Certain components present in tobacco stimulate hepatic metabolism through induction of specific cytochrome P-450 isoforms (Marcolin, 1998; McMillan & Tyndale, 2018). Consequently, the plasma concentration of drugs that undergo predominantly hepatic metabolism will change, potentially impairing pharmacotherapy.

Interactions of tobacco and psychiatric drugs can be pharmacokinetic, involving biotransformation or metabolization, or pharmacodynamic, mainly associated with nicotine, among some psychiatric drugs. In pharmacokinetic interactions, the main culprits are other tobacco compounds, more precisely polycyclic aromatic hydrocarbons, especially benzopyrene, anthracene and phenanthrene, present in the tar of cigarette smoke (Galli & Feijoó, 2002).

According to Anderson and Chan (2016), smoking primarily induces cytochrome P450 (CYP) 1A2 through activation of the aromatic hydrocarbon receptor, and to a lesser extent, CYP 2D6. Polycyclic aromatic hydrocarbons act to induce enzymes such as some glucuronosyl transferases (De Lucia & Oliveira-Filho, 2004). Other components of tobacco can also generate pharmacokinetic interactions with certain molecules. The inhibition of cytochrome isoforms, especially CYP (2D6) by oxide, is well established by *in vitro* (Gaudoneix, Taieb, Beauverie & Poisson, 2001) and *in vivo* studies (Khokhar et al., 2010).

There is special concern among mental health regarding smoking by patients with psychiatric disorders (Calheiros, Oliveira & Andretta, 2006). From the behavioral point of view, smoking is related to mood swings, exacerbation of anxiety, impaired cognition and withdrawal symptoms. From the pharmacological point of view, smoking can compromise pharmacotherapy, reducing the therapeutic effect and aggravating the adverse effects of several drugs used for treatment in psychiatry (Malbergier & De Oliveira, 2005).

Furthermore, considering the potential for tobacco-drug interactions, it is important for health professionals to be qualified to make decisions when conducting pharmacotherapy. Thus, this article discusses potential interactions between tobacco and psychiatric drugs, as well providing an overview of psychiatric diseases in the context of the COVID-19 pandemic.

2. Methodology

2.1 Integrative Review Steps

The integrative review method is the only approach that allows for the combination of diverse methodologies (for example, experimental and non-experimental research), and has the potential to play a greater role in evidence-based practice (Whittemore & Knafl, 2005).

For this review, five steps of the integrative review development process were considered (Toronto & Remington, 2020), namely: (1) elaboration of the guiding question, (2) literature search or sampling, (3) evaluation of data, (4) data analysis, and (5) interpretation and presentation of results.

2.2 Processing the Integrative Review Steps

In step 1 the following guiding questions were considered: “Is there tobacco use related to mental disorders in the period of the COVID-19 pandemic?” “Is there a pharmacological interaction between tobacco and psychoactive drugs that leads to interference with the therapeutic response of the drugs?” In step 2, for the search that involved “COVID-19, tobacco use and psychiatric illness”, articles published from December 2019 to May 2021 with online publication were considered. For the search that involved “classes of psychotropic drugs and tobacco associated with CYP450 isoforms and genetic polymorphism”, articles from 1999 to May 2021 were considered.

A literature search was performed in the Medline (via Pubmed) and Bireme databases, without year or language restrictions. Duplicate articles were already excluded in the initial search process in the databases used. For this reason, the number of excluded articles was not mentioned. The search was performed by three reviewers independently and the process was divided into three steps.

In the first step, the objective was to retrieve articles involving the interplay of COVID-19, tobacco and psychiatric illnesses. Therefore, the following keywords were used with the Boolean operator AND: (1) COVID-19, tobacco, depression; (2) COVID-19, tobacco, psychosis; (3) COVID-19, tobacco, bipolar disorder; and (4) COVID-19, tobacco, anxiety.

In the second step, we searched for articles that addressed interactions between the main pharmacological classes of psychotropic drugs with tobacco in association with CYP450 isoforms. For this, the following search strategies were used: (1) tobacco, cytochrome P-450, antidepressant; (2) tobacco, cytochrome P-450, antipsychotic; (3) tobacco, cytochrome P-450,

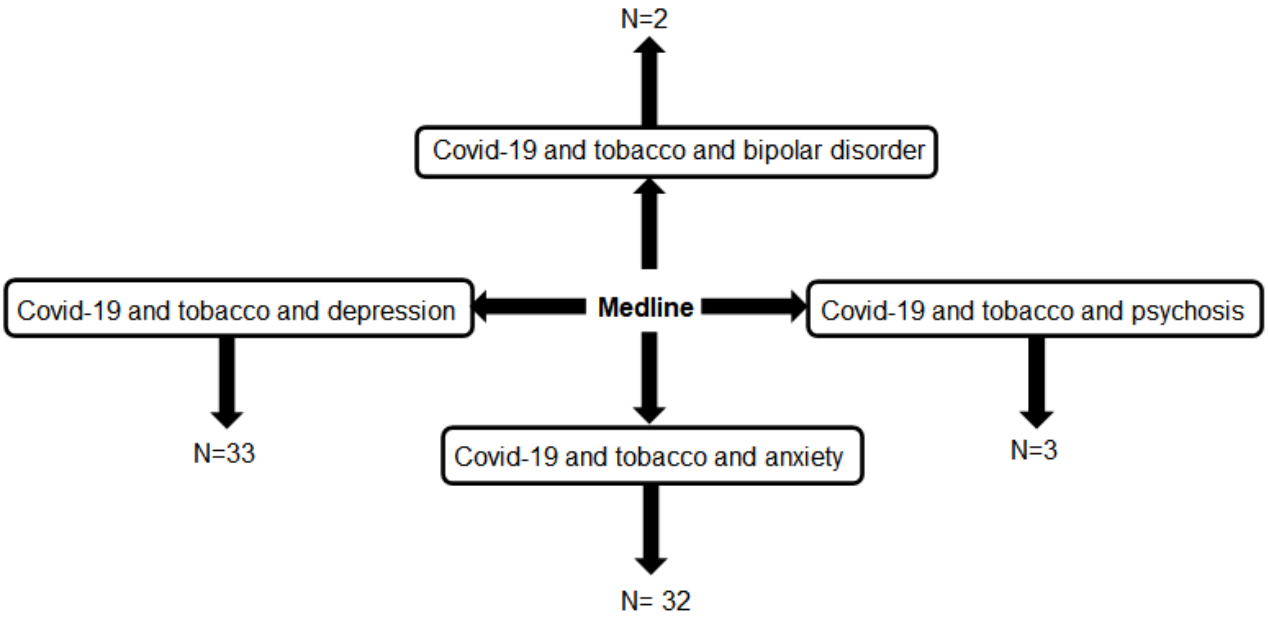
anxiolytic; and (4) tobacco, cytochrome P-450, mood stabilizer. The search strategy of the third and final step added the keyword "polymorphism" accompanied by the Boolean operator AND. The results of the search are organized in tables and flow charts.

The critical analysis of the studies, the discussion and interpretation of the results, and the presentation of the integrative review, clearly reporting the evidence found are displayed in the results, discussion, and conclusion of this scientific paper.

3. Results and Discussion

Step 1, which retrieved a total of 47 articles, is depicted in Figure 1. Articles were retrieved that addressed: bipolar disorder (n=2), psychosis (n=3), anxiety (n=32), and depression (n=33).

Figure 1. Flowchart for step 1 of the article search in the Medline database.



Source: Authors.

All articles described psychiatric disorders in the context of the COVID-19 pandemic and smoking. These articles are described in Table 1, along with others dealing with mental health and tobacco use.

Table 1. Studies addressing psychiatric disorders in the context of the COVID-19 pandemic.

Study Characteristics	Results	References
Severity factor analysis of psychological distress during the pandemic: depression.	Mild: 175 (11.7%); Moderate: 206 (13.8%); Severe: 79 (5.3%); Extremely severe: 111 (7.4%).	Stanton et al., 2020.
Observational, cross-sectional study.	Anxiety/Depression: 53 (24.9%) respondents were associated with reduced physical activity during the pandemic.	Romero-Blanco et al., 2020.
Population-based study via random telephone contact.	Smokers: 280 (18.6%), were found to have increased smoking during the pandemic (OR 2.37; 95% CI 1.08 to 5.20) associated with incorrect information that cigarette smoking protects against COVID-19.	Luk et al., 2020.
Cross-sectional study: analysis of the severity of depression.	Students: Low: 432 (50%); Mild: 214 (24.8%); Moderate: 125 (14.5%); Severe-moderate: 60 (7%); Severe: 32 (3.7%) Students' Families: Minimal: 129 (51.6%); Mild: 57 (22.8%); Moderate: 39 (15.6%); Severe-moderate: 17 (6.8%); Severe: 8 (3.2%)	Mechili et al., 2020.

Cross-sectional study to assess the prevalence of depression and anxiety in chronic patients in the midst of the pandemic in a hospital in Ethiopia.	Depression: 236 (55.7%) and Anxiety: 261 (61.8%).	Hajure et al., 2020.
Convenience sample to analyze changes in health behavior during the pandemic and the "stay at home" order in United States of America.	Depression: None or mild: 1474 (81.5%); Moderate or severe: 335 (18.5%) Tobacco use: Increased among smokers: 54 (30.5%).	Knell et al., 2020.
National survey in France among oncology patients undergoing radioactive therapy, using the Hospital Anxiety and Depression Scale.	Anxiety: 66 (32%); Depression: 35 (17%); Smoking: 29 (14.1%); Tobacco consumption increased 31%.	Hilmi et al., 2020.
Remote anonymous survey in Spain comparing control population with population exhibiting mental illness in the lockdown period.	Tobacco use: increased in 51 (12.3%) individuals in the control population and in 41 (19.9%) individuals in the mentally ill population; increased in 10 (20%) individuals with anxiety and depression; increased in 29 (19.6%) individuals with bipolar disorder and schizophrenia-related disorders Affective temperament: depressive: 32 (8.1%) in the control population and 59 (29.5%) in the mentally ill population; anxious: 71 (17.7%) in the control population and 61 (30%) in the mentally ill population; depressive-anxious: 16 (4.1%) in the control population and 32 (16.1%) in the mentally ill population Psychiatric diagnosis variables (population with mental illness): depression: 20 (9.7%); anxiety: 30 (14.5%); bipolar disorder: 114 (55.3%); schizoaffective disorder: 15 (7.2%); psychotic disorders: 10 (4.8%); schizophrenia: 9 (4.3%).	Solé et al., 2021.
Literature review that discussed the benefit/risk ratio of psychotropic treatments for people with psychological distress due to COVID-19.	To date, there is no international recommendation for the adaptation of pharmacotherapy of psychiatric disorders due to SARS-CoV 19 infection, except for the use of clozapine, which is associated with an increased risk of pneumonia.	Javelot et al., 2020.
Case series with 3 participants who stopped using tobacco due to the pandemic.	3 patients from a mental health outpatient clinic with psychotic disorder reported a desire to quit smoking. The evaluation showed that such motivation arose because of COVID-19. After one week of reporting, 1 patient returned to smoking and the other 2 returned after 4 weeks. In common, all 3 patients reported tobacco use as a protective factor against SARS-CoV-19 infection and reported that this information was shared in videos and newspapers.	Theuerkauff & Hanak, 2020.
Review of literature that linked abuse of different substances (tobacco, opioids and alcohol) with COVID-19.	Direct relationship between smoking and the incidence of COVID-19 infection and its severity. Stress from the pandemic scenario is one of the main causes for relapse to drug use in people with a history of substance abuse disorders. The possible increase in cigarette consumption during lockdown was associated with younger age, current living situation, lower education, lack of social contacts, boredom, reward after a hard day's work, loss of daily structure, loneliness, and conviviality.	Althobaiti et al., 2020.
Online survey in France assessing changes in participants' behavior and mental state during confinement.	1454 individuals aged 24 to 65 years participated in the study. Confinement had a negative effect on all behaviors assessed except nutrition. 11.2% of the participants reported an increase in tobacco use, versus 6.3% who reported a decrease. 50.6% of individuals reported being more depressed, stressed, or angry since the beginning of the lockdown.	Rossinot et al., 2020.
A cross-sectional study that assessed factors associated with alcohol and tobacco consumption as a strategy to confront the pandemic in Spain.	21,207 individuals participated in the study. 13.5% of the participants reported using alcohol, 12% tobacco, and 6.5% both substances as a coping strategy for the pandemic. Having a current mental disorder was associated with tobacco use as a coping strategy [OR = 1.391, $p < 0.001$]. According to the DASS-21 scale, 45.6%, 52.5%, and 54.7% of the sample using alcohol, tobacco, or both, respectively, as a form of coping had mild, moderate, severe, or extremely severe depression. 9.4%, 15.2% and 14.2% of the respondents using alcohol, tobacco or both, respectively, as a form of coping could be considered as having mild, moderate, severe or extremely severe anxiety on the DASS-21 scale.	Martínez-Cao et al., 2021.

Analysis of the use of alcohol and other substances among pregnant women during the COVID-19 pandemic.	Use during pregnancy: alcohol (6.7%); marijuana (4.3%); tobacco (4.9%); illicit drugs (0.3%); multiple substances (2.6%). Symptoms of depression and financial difficulties were associated with increased use of tobacco, cannabis, and multiple substances.	Kar et al., 2021.
Cross-sectional survey that assessed the prevalence of changing substance use patterns during the pandemic.	Among the 542 respondents, 34.3% reported a change in their usage patterns during the pandemic. Among these, 47.3% reported a reduction in tobacco use due to COVID-19. Substance use changed significantly for respondents who had anxiety (58.1%; prevalence ratio = 1.45; 95% CI) and depression (55.9%; prevalence ratio = 1.44; 95% CI).	Sharma et al., 2020.
Multinational surveillance program conducted in South Asia to analyze knowledge, behaviors, and health and socioeconomic circumstances during the lockdown.	29,809 adult men and women participated in the study. Tobacco use dropped 41% (from 24.4% to 14.5%) compared to pre-pandemic levels. About 40% of participants reported symptoms of anxiety or depression. The prevalence of anxiety and depression was higher in the 30 to 49 age group, among people with chronic diseases, and in people with lower education and income.	Kusuma et al., 2021.
Retrospective cohort study: assessing the prevalence of concomitant psychiatric conditions in the orthopedic trauma population during the COVID-19 pandemic.	553 orthopedic patients participated in the study. Higher prevalence of mental health diagnoses (26% vs. 43%) among patients in the 2020 cohort compared to the 2019 group. Smoking rates were not significantly different between the two groups. There were increased rates of depression (n = 47 vs. N = 34) and anxiety (n = 21 vs. n = 7).	Ohliger et al., 2020.
Cross-sectional online survey: assessing changes in lifestyle habits, treatment adherence and mental health status in patients with cardiometabolic disease.	4,216 patients from 13 Spanish-speaking Latin American countries participated in the survey. 17% of smokers reported increased tobacco use, and 52.3% reported having considered quitting. Perceived depression was reported by 41.5% of participants and was associated with low education and low income.	Santi et al., 2021.
Cross-sectional study: to assess anxiety among the population of Andhra Pradesh using the COVID-19 Anxiety Scale (CAS-7).	1,346 subjects participated in the study. The mean CAS-7 score was 18.9 ± 6.4. Smokers and current alcohol users had higher scores compared to non-users (22.1 ± 5.3 vs. 18.4 ± 6.7 and 21.9 ± 4.9 vs. 18.5 ± 7.2, respectively).	Meesala et al., 2020.
Online cross-sectional survey: assessing changes in tobacco and alcohol consumption in the French population after the lockdown.	2003 individuals participated in the survey. Among the total sample, 21.5% and 19.9% reported probable anxiety level and depressed mood, respectively. Among current smokers, 26.7% reported an increase in tobacco use since blocking. 29.0% of smokers had a probable level of anxiety, while 24.6% of smokers reported probable depression according to the HADS.	Guignard et al., 2021.
A national online survey conducted in the US collecting data on COVID-19 related to knowledge, awareness, adoption of preventive practices, depression, anxiety, pessimism, and tobacco and alcohol use.	4,998 people completed the survey. Among smokers (n =1359), 22% reported increased tobacco use. 44% of respondents scored consistently with depression and anxiety, and 52% reported high stress scores. COVID-19-related anxiety and depression were associated with increased smoking (AOR = 2.17; 95% CI = 1.64, 2.88). High stress scores were also associated with increased smoking (AOR = 1.75; 95% CI = 1.31, 2.33).	DiClemente et al., 2021.
Online survey: assessing health risk behaviors before and during the COVID-19 pandemic.	5,021 students from four German universities participated in the survey. Tobacco use: about 19% of students reported smoking, with 13% smoking cigarettes more than once a week before and during the COVID-19 pandemic. Before the COVID-19 pandemic, 85% smoked no cigarettes, 10% 1-9 cigarettes, 4% 10-19 cigarettes, and 1% more than 20 cigarettes per day. These proportions did not change substantially during the pandemic. Depressive symptoms are among the factors associated with increased health risk behaviors but are also associated with a reduction in tobacco use during the COVID-19 pandemic.	Busse et al., 2021.
Online survey: assessing factors associated with changes in mood and anxiety among young males during the pandemic.	571 male adolescents and young adults completed the survey. 31.6% of participants reported that their mood had worsened, or their anxiety had increased (32.3%) during the pandemic. Factors associated with worsening mood and increased anxiety: high family socioeconomic status; older age; decreased proximity to friends and family; and negative mental health impact of COVID-19. Factors associated only with increased anxiety: history of symptoms of depression and anxiety.	Tetreault et al., 2021.

Online retrospective survey: assessing changes in health behaviors among students at a French university during the lockdown.	3671 students participated in the survey. The main stressors for students were change in teaching methods (56.9%); non-validation of the school year (44.1%); and the increase in course load (37.4%). There was a significant decrease in smoking prevalence (18.5% to 14.8%). Unfavorable changes in smoking (2.0%) were associated with higher levels of depression and concern about not being able to validate the school year.	Tavolacci et al., 2021.
Online survey: to assess the prevalence of symptoms of depression, anxiety and stress, and behavioral aspects in the Brazilian population during the COVID-19 pandemic.	3,000 people participated in the survey. Almost half of the participants expressed symptoms of depression (46.4%), anxiety (39.7%) and stress (42.2%). These were highest in women, people without children, students, patients with chronic diseases, and people who had contact with other people diagnosed with COVID-19. 40.8% of respondents perceived increased intake of food, alcohol, drugs, tobacco, and medications.	Serafim et al., 2021.
Observational study to evaluate factors associated with changes in alcohol and tobacco use during the lockdown.	1,362 subjects participated in the study, of whom 26.0% were smokers. Smokers: 60.9% reported no change in consumption. 30.5% reported increased consumption. Factors associated with increased smoking: feeling very nervous (aOR 2.2, 95% CI 1.2-4.0, P = 0.009); feeling despondent/depressed (aOR 2.4, 95% CI 1.3-4.4, P = 0.004); being concerned about someone else's health (aOR 2.0, 95% CI 1.1-3.9, P = 0.031); working at home (aOR 2.3, 95% CI 1.0-5.3, P = 0.046); and increased alcohol consumption (aOR 3.6, 95% CI 1.7-7.7, P = 0.023).	Reynolds et al., 2021.
Multicenter cross-sectional study assessing the prevalence of mental health problems and substance use in migrant workers.	275 migrant workers and 276 non-displaced migrants from four cities in India participated in the study. The prevalence of ever using all substances among migrants was 44.4%, while among the non-displaced group it was 45.3%. Tobacco was the most commonly used substance. The prevalence of at least one diagnosis on the PHQ-9 in reverse migrants was 19.3%, and in non-displaced migrants it was 7.6%. The prevalence of another depressive disorder in migrants was higher than in non-displaced migrants (17.1% vs. 4.0%).	Chavan et al., 2022.
Cross-sectional study assessing the impact of lockdown on individuals in treatment for substance abuse disorders.	303 individuals participated in the survey. 9.5% of patients reduced the frequency of tobacco use during lockdown, while 5.4% of patients reported an increase (n = 294). 58.7% of the sample had clinical anxiety symptoms, and 48.2% of participants scored above the clinical threshold for depression. 50.3% reported worsening depression and anxiety symptoms during lockdown, associated with the following risk factors: prior trauma exposure, female gender, distress and isolation, reduced income, and alcohol use.	Blithikioti, Nuño, Paniello, Gual, & Miquel, 2021.
Prevalence study with analysis of factors associated with the increase in cigarette consumption in the Brazilian population.	The prevalence of smokers in the population was 12%, with 34% of smokers reporting increased cigarette consumption. Increased cigarette smoking was associated with poorer sleep quality, feeling isolated from family members, feeling sad or depressed, feeling anxious, insufficient income, and poorer health status.	Malta et al., 2021.
Cross-sectional, correlational study assessing the sleep quality of Tunisian medical students during confinement due to the pandemic.	72.5% of medical students were considered poor sleepers. Factors contributing to poor sleep quality were family history of suicide attempts, tobacco use, perceived home confinement, reduced physical activity, anxiety, and hopelessness.	Saguem et al., 2022.
Systematic review that explored health interventions at universities plus the impact and contributions to the mental health landscape during the the COVID-19 pandemic.	Mobile interventions showed promising results for reducing psychological symptomatology associated with stress, depression, anxiety, and general mental health in students. In the context of the COVID-19 pandemic, this health strategy can facilitate professionals' contact with the patient at a safe distance, avoiding treatment interruption.	Oliveira et al., 2021.
Cross-sectional study: analyze suicidal behavior among Mexican adolescents in confinement due to the COVID-19 pandemic.	8,033 high school students participated in the study. One in five students experienced suicidal behavior (20.5%; self-harm, 5.7%; low lethality suicide attempt, 11.2%; high lethality suicide attempt, 3.6%). Variables associated with higher odds of suicidal behavior included: female gender, depression, hopelessness, anxiety, alcohol and tobacco use, childhood trauma, and self-confidence as issues affecting attachment and low self-esteem.	Hermosillo-de-la-Torre et al., 2021.

Observational clinical study to investigate the effect of COVID-19 on levels of stress, anxiety and depression, as well as withdrawal symptoms and craving and substance use in patients using methadone.	The impact of the COVID-19 outbreaks in Wuhan (China) on patients receiving methadone maintenance treatment for heroin addiction was negative, which increased the patients' drug cravings and risk of relapse. These patients showed high levels of psychological stress, anxiety, and depression during the pandemic. The fear caused by COVID-19 reduced income, loneliness. The loss of family members due to the epidemic was also an important factor that caused negative emotions in patients, acting as negative reinforcing factors. There was an increase in tobacco consumption during the outbreak and in the post-epidemic period.	Liu et al., 2021.
Analysis of the impact of the pandemic on tobacco use in college students from contacted patients who participated in a longitudinal study of associated alcohol and marijuana use.	A sample of 83 participants reported tobacco use in the week prior to campus closure related to COVID-19. This sample included patients who reported cigarette (n= 35) and/or e-cigarette (n= 69) use. The frequency of smoking and vaporizing decreased compared to the period prior to campus closure. However, the decrease in frequency did not correspond to the decrease in quantity. 24 participants (28.9%) discontinued use since campus closure. Greater symptoms of generalized anxiety and moving to a non-independent residence (versus remaining independent) were related to the greater chances of discontinuation. Exposure to and searching for COVID-19 related news were associated with reduced odds of breaks.	Sokolovsky et al., 2021.
Analysis of the prevalence of substance abuse in India.	30,354 individuals who use tobacco and 30,159 individuals who abuse alcohol participated in the study. Prevalence: about 8.7% for alcohol abuse and 7.9% for tobacco abuse.	Sivapuram et al., 2020.
A cross-sectional study that assessed the prevalence of anxiety and associated factors during confinement.	3,936 French students participated in the study. Moderate anxiety: 15.2%; severe anxiety: 9.8%. Factors associated with moderate to severe anxiety: female gender (OR = 2.2, 95% CI: 1.8-2.7); having relatives or acquaintances from their residences hospitalized for COVID-19 (OR = 3.3, 95% CI: 1.4-7.9); tensions at home (OR = 1.8, 95% CI: 1.5-2.1); isolation difficulties (OR = 1.4, 95% CI: 1.1-1.6); noises inside (OR = 1.6, 95% CI: 1.3-1.9) or outside the housing site (OR = 1.5, 95% CI: 1.3-1.8); no direct private access to outdoors via a garden, terrace, or balcony (OR = 1.6, 95% CI: 1.3-2.0); delayed final exam (OR = 1.6, 95% CI: 1.3-2.1) and reduced time for learning due to academic interruption (OR = 1.3, 95% CI: 1.1-1.6); increased smoking (OR = 1.9, 95% CI: 1.4- 2. 6); ineffective use of media entertainment (OR = 2.2, 95% CI: 1.1-4.4) and reading (OR = 1.9, 95% CI: 1.3-2.7) to calm down. Support from family (OR = 0.85, 95% CI: 0.8-0.91) and friend (OR = 0.88, 95% CI: 0.82-0.94) were protective factors.	Bourion-Bédès et al., 2021.
Qualitative study identifying the motivators of changes in tobacco use at the onset of lockdown, from semi-structured telephone interviews.	Increased tobacco use was most common and predominantly driven by individual-level factors: pandemic-related anxiety, boredom, and irregular routines. Decreased consumption was common among social users, who reported fewer interpersonal interactions and fear. Retail access impacted the use of cigarettes and electronic nicotine release systems (vaporizers). Due to more limited access to vaporizers, some individuals shifted to online purchases. Delivery delays led some of these users to compensate with cigarettes, which were more affordable.	Giovenco et al., 2021.
Psychometric study assessing the level of fear associated with COVID-19.	431 Turks participated in the study. The overall scores of the participants on the Fear of COVID-19 Scale (FCV-19S) were equal to 21.47 ± 6.28. Therefore, the level of fear of COVID-19 infection in the Turkish population was high. 26.7% of the participants were smokers. Tobacco use did not affect the fear of contracting Coronavirus-19 infection (FCV-19S score: smokers= 20.16 ± 7.10; nonsmokers = 20.28 ± 6.82. $p > 0.05$). 80.7% of participants reported being afraid to go to the hospital during the COVID-19 outbreak (FCV-19S score: individuals who had anxiety about going to the hospital during the outbreak= 22.06 ± 7.46; no anxiety = 19.86 ± 6.71. $p > 0.05$).	Korukcu et al., 2021.

Remote research that assessed changes in alcohol and tobacco consumption during the pandemic.	3,245 Germans participated in the survey. 35.5% of participants reported an increase in alcohol consumption during the lockdown (42.9% did not change their drinking behavior, 21.3% drank less, and 0.3% started drinking). 45.8% of smoking participants increased their tobacco consumption, 4.0% started smoking, 9.0% smoked less, and 9.9% stopped smoking during the lockdown. Factors associated with increased alcohol consumption: middle age, greater subjective stress due to the COVID-19 pandemic; lower agreement with the importance of restrictions; and alcohol consumption more than once a week before the lockdown. Factor associated with increased smoking: greater subjective stress due to the COVID-19 pandemic.	Koopmann et al., 2021.
Single-center cross-sectional survey that evaluated changes in tobacco use in outpatients of a clinic with a stop smoking program.	114 volunteers participated in the survey. Tobacco consumption: 38.6% were unable to continue in the smoking cessation clinic because of the pandemic; 35% returned to smoking after smoking cessation; 2% stopped smoking and managed not to relapse. Patients who tried to quit smoking, but relapsed went an average of 3.7 months without smoking. Anxiety due to COVID-19 and restrictions (coronaphobia): 56.1% Yes; 43.9% No. People with coronaphobia exhibited significantly greater decrease or cessation of smoking compared to no change in smoking behavior or increase in number of cigarettes (p= 0.006).	Ozcelik & Yilmaz, 2021.
Analysis of tobacco use before and during lockdown in New Zealand from online panel data from a demographically representative sample.	261 respondents reported smoking every day and another 71 reported smoking at least once a week, but not daily. Daily smokers: 45% smoked more during the lockdown, increased by an average of 6.2 cigarettes (from 10.1 per day to 16.3, p <0.001); 39% did not change consumption; 16% reported smoking fewer cigarettes per day, decreased by an average of 5.0 cigarettes (from 11.2 per day to 6.2, p = 0.001). Weekly smokers: 34% smoked more during the lockdown, increased by an average of 8.6 cigarettes (6.4 per week to 15.0, p = 0.020); 27% reported smoking the same number of cigarettes; 39% smoked fewer cigarettes, decreased by an average of 6.5 cigarettes (from 13.8 per week to 7.3, p = 0.039). Factors associated with increased daily consumption: loneliness and isolation (Adj OR 3.65, 95% CI 1.35-9.86).	Gendall et al., 2021.
Analysis of changes in tobacco use due to the pandemic and determining the impact of psychosocial factors on this behavior.	The sample size was 4,075 respondents. The prevalence of current smoking was 16.0%. Many respondents reported that the pandemic had a negative impact on their mental health and the impact was more pronounced among those who smoked more. Current smokers (n= 329): 25.2% (n= 86) reported smoking more than usual; 50.9% (n= 174) reported smoking the same amount; and 20.2% (n= 69) reported smoking less. Psychosocial factors associated with increased tobacco use: concern about their mental health (42.3%); anxiety (40.2%); stress (36.9%); bad mood (32.2%).	Tzu-Hsuan Chen, 2020.
Evaluation of strategies used by mental health professionals to manage anxiety/distress associated with COVID-19, as well as the perceived effectiveness of these strategies.	888 individuals participated in the study. Behavioral strategies were the most common, such as: distraction/engaging in an enjoyable activity (88.63%); spending time with loved ones (77.82%); and exercise (72.64%). 28.27% and 2.14% reported using alcohol and tobacco, respectively, as a coping strategy.	Reilly et al., 2021.
Prospective observational study that assessed changes in mental and behavioral responses during the COVID-19 epidemic.	102 individuals participated in the study. A statistically significant decreasing trend was observed in the mean scores for mental stress, emotional state, and lifestyle from the beginning to the conclusion of the study (mental stress: 27.60 vs 24.57; emotional state: 1.48 vs 1.16; lifestyle: 1.45 vs 1.25). Factors associated with mental stress, emotional state, and lifestyle: number of new confirmed patients reported in China [β = 0.008 (p<0.01), 0.009 (p<0.01) and 0.006 (p<0.05), respectively]; perceived high risk [β = 2.341 (p<0.01), 0.153 (p<0.01) and 0.043 (p<0.05), respectively]; perceived severity [β= 0.972 (p<0.01), 0.820 (p<0.01) and 1.903 (p<0.01).	Yang et al., 2021.

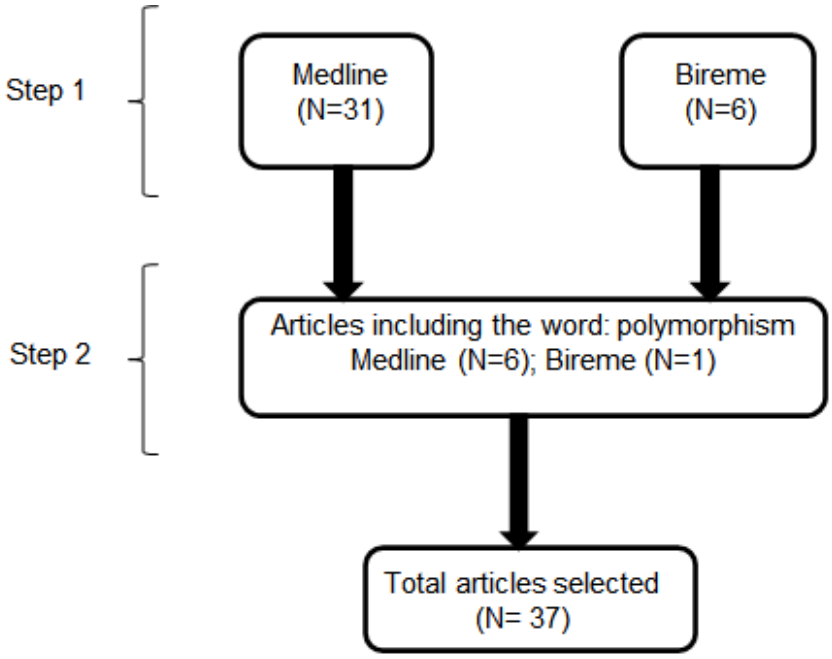
	The longer people were confined in their homes, the worse their emotional and lifestyle status was [β = 0.027 ($p<0.05$) and 0.024 ($p<0.05$)].	
Online survey that assessed the impact of the pandemic on substance abuse, mental health, and weight-related behaviors in obese patients.	589 patients participated in the survey. 48.4% reported recreational substance use: 24.3% opioids; 9.5% sedatives/tranquilizers; 3.6% marijuana; 1% stimulants; 6% tobacco. 9.8% reported increased use since the start of the pandemic. Main reasons for this increased use: 71.9% stress; 64.9% anxiety; 40.4% depression; 49.1% boredom; 50.9% coping mechanism. 68.6% reported that it was more difficult to achieve their weight loss goals during the pandemic. 50.3% reported a decrease in the amount of time for exercise, and 53.6% reported a decrease in exercise intensity. Non-substance users reported increased exercise intensity compared to substance users (7.2% versus 3.3%, p= 0.029). The majority of the sample reported difficulty falling asleep (62.8%), anxiety (64.5%), and depression (81.4%). Differences between substance use groups were significant for difficulty falling asleep (substance users 32.7% versus non-users 30.1%, p= 0.032).	Almandoz et al., 2021.
Analysis of the relationship between COVID-19 concern and coping strategies for smoking, perceived barriers to smoking cessation, and expectations of smoking abstinence.	219 daily cigarette smokers participated in the study. Concern about COVID-19 was significantly and positively related to COVID-19 coping motives for smoking and perceived barriers to smoking cessation. Factors associated with COVID-19 concern: major cognitive-affective processes of smoking, age, sex, race, ethnicity, COVID-19 exposure, smoking rate, e-cigarette use, and anxiety symptoms.	Shepherd et al., 2021.
Online survey that assessed the determinants of change in health practices (diet and physical activity) and addictive activities (alcohol, smoking, and vapor use) during lockdown.	1276 individuals participated in the survey. Regarding healthy lifestyle behaviors, 36% increased healthy eating behaviors and 33% increased physical activity. For unhealthy lifestyle behaviors, 40% of respondents reported increases in alcohol consumption, 41% reported increases in smoking, and 46% reported increases in smoking since the start of the pandemic. Individuals who had anxiety were more likely to report increases in addictive behaviors since the start of the pandemic compared to those who did not have anxiety (β = 0.26, 95% CI 0.09 to 0.43).	Zhang et al., 2021.

Source: Authors.

3.1 Interactions Between Tobacco and Antidepressants

From the search in step 2, 31 articles were retrieved for the antidepressant pharmacological group in the Medline database. Also in step 2, by searching the Bireme database, 6 articles were found for the interaction of tobacco, cytochrome P450, and antidepressants, totaling 37 articles. In step 3, 6 articles were found in the Medline database and 1 article in the Bireme database for the interaction of tobacco, cytochrome P450, antidepressant, and polymorphism. Figure 2 describes the findings of these steps.

Figure 2. Flowchart of the search for articles addressing interactions between tobacco and antidepressants.



Source: Authors.

The Table 2 describes pharmacokinetic interaction involving cytochrome P-450 (CYP-450) between tobacco and antidepressant drugs.

Table 2. Pharmacokinetic interaction involving cytochrome P-450 (CYP-450) between tobacco and antidepressant drugs.

Antidepressant Drugs	Cytochrome P-450	Consequence	Study Characteristic	References
Amitriptyline	CYP1A2 and CYP2D6	Enzyme induction; reduction of drug effect.	Naturalistic clinical setting (n=503); p=0.038 (comparing smokers to nonsmokers treated with amitriptyline).	Scherf-Clavel et al., 2019a.
Imipramine	CYP1A2 and CYP2D6	Enzyme induction; reduction of drug effect.	Case report.	Gressier et al., 2015.
Escitalopram	CYP1A2, CYP2C19 and CYP3A4	Enzyme induction; reduction of drug effect.	Observational study (n=36, smokers; n=88 nonsmokers; p=0.027 (comparing smokers to nonsmokers treated with escitalopram).	Scherf-Clavel et al., 2019b.
Mirtazapine	CYP1A2 and CYP2C19	Enzyme induction; reduction of drug effect.	Naturalistic clinical setting (n=572); p=0.002 (comparing smokers to non-smokers) treated with mirtazapine).	Scherf-Clavel et al., 2019a.
Duloxetine	CYP1A2	Enzyme induction; reduction of drug effect.	Naturalistic clinical setting (n=125); p=0.002 (comparing smokers to nonsmokers treated with duloxetine).	Augustin et al., 2018.

Source: Authors.

Depression is one of the psychiatric comorbidities most associated with smoking. It is the subject of several studies conducted in recent years to elucidate this coalition. According to Calheiros et al. (2006), there is a bidirectional relationship between nicotine and depression, with emphasis on the actions of nicotine in the brain, where nicotine can regulate the

transmission of various neurochemical systems, including dopamine, gamma-aminobutyric acid, and glutamate, in various mesocorticolimbic structures involved in mental disorders (Laviolette, 2021). In this sense, smoking may be a form of self-medication by the patient to combat feelings of sadness or improve mood, thus reinforcing the desire to smoke. A prospective cohort study conducted by Flensborg-Masdsen and colleagues (2011) showed that women who smoke more than 10 g of tobacco per day and men who smoke more than 20 g per day had significantly higher risks of depression compared to nonsmokers.

These patients encounter serious difficulties in their attempts to quit or reduce smoking, because there is a dilemma: tobacco abstinence can facilitate the development of severe cases of depression, since nicotine helps maintain the internal homeostasis of the individual, and the lack of nicotine leads to an increase in negative signs such as depressed mood, nervousness and restlessness, among others, generating frequent relapses (Calheiros et al., 2006; Freire et al. 2007; da Costa, Cotrik, Araújo, & Brasil, 2013).

Tricyclic antidepressants (TADs), among them amitriptyline, imipramine and clomipramine, are metabolized by CYP (1A2) and (2D6), and some substances can increase their clearance from 50 to 100%. The effect of smoking on the metabolism of TADs is small, around 15%, but in general these have a low therapeutic index and five mechanisms of action. Thus, small changes in their plasma concentration can result in numerous undesirable effects. Therefore, the efficiency of the pharmacotherapy with TADs employed in many patients who smoke can decrease, and its effects exacerbated with its abrupt withdrawal, thus requiring dose adjustments (Marcolin 1998; Gaudoneix et al., 2001).

Smokers who quit smoking face depressive episodes for approximately nine months. This risk is 2% in people with no depressive history, 17% in people with a history of a single episode, and up to 30% in recurrent depressives (Sobradiel & García-Vicent, 2007).

3.2 Interactions Between Tobacco and Antipsychotics

Step 2 retrieved 19 articles from the antipsychotic pharmacological group in the Medline database. Also in step 2, searching the Bireme database did not find any articles on the interaction among tobacco, cytochrome P450 and antipsychotic, while 4 were found in the Medline database. The Table 3 describes pharmacokinetic interaction involving cytochrome P-450 (CYP-450) between tobacco and antipsychotic drugs.

Table 3. Pharmacokinetic interaction involving cytochrome P-450 (CYP-450) between tobacco and antipsychotic drugs.

Antipsychotic Drugs	Cytochrome P-450	Consequence	Study Characteristic	References
Clozapine	[a]CYP1A2 and CYP2C19	Enzyme induction; reduction of drug effect.	[1]Naturalistic clinical setting (n=106); P=0.02 (comparing smokers with nonsmokers treated with clozapine). [2]Review.	[1] Scherf-Clavel et al. 2019a; [2]Kroon 2007; [2]Dervaux & Laqueille, 2007; [2]Ivanova et al., 2015.
Risperidone	CYP1A2 and CYP3A4	Enzyme induction produced by polycyclic aromatic polycarbons; reduction of drug effect.	Naturalistic clinical setting (n=401, smokers and n=292 nonsmokers); P=0.001 (comparing smokers to nonsmokers treated with risperidone).	Schoretsanitis et al., 2017.
Olanzapine	CYP1A2	Enzyme induction; reduction of drug effect.	[1]Review.	[1]Callaghan, Bergstrom, Ptak, & Beasley, 1999; [1] Kroon 2007; [1]Dervaux & Laqueille, 2007.
Cholpromazine	CYP1A2	Enzyme induction; reduction of drug effect.	Review.	Dervaux & Laqueille, 2007.

Haloperidol	CYP1A2	Enzyme induction; reduction of drug effect.	Review.	Dervaux & Laqueille, 2007.
Thioridazine	CYP2D6	Enzyme induction; reduction of drug effect.	Observational study (n=58 smokers and n=18 nonsmokers); p<0.001 comparing smokers with nonsmokers treated with thioridazine).	Berecz et al., 2003.

[(a)]Polymorphism in CYP1A2*1F. Source: Authors.

Tobacco consumption among psychotic patients is approximately 74% for outpatients and 88% for inpatients, exceeding 90% for chronic institutionalized patients, most with moderate to severe dependence. It is established that patients diagnosed with schizophrenia and smokers have more positive symptoms, such as delusions and hallucinations; and fewer negative symptoms, such as social isolation, affective blunting and anhedonia (Sobradiel & García-Vicent 2007; Oliveira et al., 2019; Ronzani et al., 2020).

Schizophrenia has a high correlation with smoking (Heijden et al., 2021). It is estimated that about 80% of patients with schizophrenia are smokers. They also tend to be heavy smokers, consuming higher doses of nicotine and smoking a large number of cigarettes. Few ever quit smoking. Added to this, there is a poor response to treatment for nicotine dependence, as well as maintaining abstinence. For this situation, a cigarette can play an existential role of extreme importance in the patient's life (Sobradiel & García-Vicent, 2007).

The pharmacokinetic variations promoted by tobacco may require a posological adaptation, as occurs with TADs, and in some cases monitoring of patients is necessary when there is abrupt interruption of tobacco consumption (Marcolin 1998; Gaudoneix et al., 2001).

3.3 Interactions Between Tobacco and Anxiolytics

Step 2 retrieved three articles for the pharmacological group anxiolytics in the Medline database. Also in step 2, searching the Bireme database found no articles on the interaction of tobacco, cytochrome P450 and anxiolytics. In step 3, one article was found in the Medline database for the interaction of tobacco, cytochrome P450, antipsychotics, and polymorphism. No article addressing polymorphism was found in the Bireme database.

Anxiety disorders, also defined by excessive worry and fear, are debilitating, counterproductive, and are among the most common psychiatric conditions in the West (Simpson et al., 2010). Untreated anxiety has been associated with significant personal and social costs, related to frequent primary and acute care visits, decreased work productivity, unemployment, and impaired social relationships (Remes et al., 2016).

In late July 2021, the Italian Center for Monitoring Medication Use (*Osservatorio Nazionale sull'impiego dei Medicinali*) released a report on medication use during the COVID-19 pandemic (Gualano et al., 2021). When considering outpatient antidepressant consumption before (January and February 2020) and after (March and April 2020) social isolation, no significant difference was reported in the use of these medications (p=0.957). On the other hand, however, in the three-month period after social isolation, anxiolytic medications purchased privately by citizens showed a slight significant increase (p<0.001). Again, higher purchase was recorded in March, when isolation began (Gualano et al., 2021).

According to the findings of the Italian Center for Monitoring Medication Use, social isolation was an important factor for increased anxiolytic consumption, since changes in family organization and work routines, as well as home confinement, can induce feelings of helplessness, abandonment, loneliness, insomnia, and anger (Shigemura et al., 2020). Since people with mental disorders tend to consume more tobacco, drug-tobacco interactions need to be explored (Seminog & Goldacre, 2013).

Although our searches of the Medline and Bireme databases did not retrieve any relevant articles associating clinically significant drug interactions with the use of anxiolytics and tobacco concomitantly, it is important to consider the fact that the main anxiolytics used, i.e., the benzodiazepines, are metabolized by CYP450 isoforms (Otani, 2003). Therefore, drug-tobacco interactions are possible in this coadministration (Mohebbi et al., 2020).

3.4 Interactions Between Tobacco and Mood Stabilizers

Step 2 retrieved two articles for mood stabilizers from the Medline database. Also in step 2, searching the Bireme database did not locate any articles addressing the interaction among tobacco, cytochrome P450 and mood stabilizers. In step 3, one article was found in the Medline database for the interaction of tobacco, cytochrome P450, mood stabilizers, and polymorphism. Finally, no article addressing polymorphism was found in the Bireme database.

There was probably increased incidence of mental disorders during the pandemic (Ghebreyesus, 2020). Experts in psychiatry and mental health have expressed concerns that people with pre-existing mental disorder may be at increased risk of COVID-19 infection, as well as suffer worse outcomes when infected (Yao et al., 2020).

A case-control study showed that patients with recent diagnosis of mental disorder had significantly higher odds of SARS-CoV-2 infection than patients without mental disorder. Patients with bipolar disorder had a five-fold higher chance (odds ratio) of being infected compared to patients without such conditions (Wang et al., 2021).

According to Rajkumar (2020), there are certain aspects of the pandemic and the measures needed to control it that are of particular concern to patients with bipolar disorder, as follows: (1) the sensitivity of the disease course to factors that disrupt biological and social rhythms; (2) use of substances such as alcohol and tobacco, or withdrawal syndromes associated with discontinuing use of these substances, potentially leading to suicide and worsening of symptoms; and (3) increased susceptibility to infections associated with a diagnosis of bipolar disorder and other mental disorders.

Given such factors, it is notable that these patients may increase their tobacco use in association with the drugs used for disease management (Rajkumar, 2020). Therefore, like the anxiolytics previously discussed, tobacco-drug interactions may occur in this pharmacological class. Although our search did not retrieve relevant studies showing clinically significant interactions, mood stabilizers, including lithium, and therapeutic adjuvants (lamotrigine, valproic acid, and carbamazepine) are basic drugs for the treatment of patients with bipolar disorder in the acute and maintenance phase, and may have potential interactions with tobacco (Gould et al., 2002).

It is worth adding that valproic acid and carbamazepine act as enzyme inhibitors and inducers, respectively, in CYP2C9, CYP3A4; and CYP1A2, CYP2C9, and CYP3A4 (Brunton et al., 2018). On the other hand, so far no biotransformation pathways have been found in lamotrigine and lithium that include these enzymes (Hill & Lee, 2013). In this context, mental health context should pay attention to the use of these drugs concomitantly with tobacco. The worsening or lack of control of symptoms, as well as increased adverse effects, may be related to this coadministration (Mohebbi et al., 2020). Considering the risks and benefits, along with constantly monitoring these patients, are key practices for the rational use of these medications.

3.5 Fake News about Tobacco Use during the COVID-19 Pandemic

In addition to the pandemic, a growing infodemic has plagued the world (Garcia & Duarte, 2020). Among patients with psychiatric disorders, excessive false information can cause harm and worsening of health status. Theuerkauff & Hanak (2020) reported a situation in a mental health outpatient clinic of patients (n=3) with psychiatric disorders who decided to quit smoking because of the pandemic, believing smoking was a risk factor. However, weeks later all three patients had resumed smoking. When these patients were asked about this, they mentioned smoking as a protective factor against infection with the new coronavirus. The patients also reported that several online videos supported this hypothesis (Theuerkauff & Hanak, 2020).

Unsurprisingly, misleading information about the COVID-19 pandemic is commonly found and shared on the internet (D'Souza et al., 2020; Li et al., 2020b).

A meta-analysis (Patanavanich & Glantz, 2020) showed that tobacco use is associated with a worse prognosis of COVID-19. Furthermore, Berlin, Thomas, Le Faou, and Cornuz (2020) emphasized the difference between a supposed protective effect of nicotine and the known devastating effects of tobacco, showing that tobacco use is indeed a risk factor.

Thus, given the complications associated with tobacco and the comorbidities of patients with psychiatric illnesses, it is critical for healthcare professionals to encourage patients to stop smoking in this context (Theuerkauff & Hanak, 2020). Social isolation can result in mental distress, increasing the need to smoke. Therefore, health education actions should include references to the importance of smoking cessation during the pandemic, so that people do not rely on false information, and instead are supported by the best scientific evidence (Berlin et al., 2020).

3.6 Therapeutic Adaptations

The pandemic has brought a number of challenges to healthcare professionals and systems. In this uncertain environment, multiple recommendations are issued, but it is necessary to verify their scientific validity and ensure applicability according to the reality in which the problem is embedded (Javelot et al., 2020). The serious risk factors inherent to SARS-CoV-2 infection are mainly: age, male gender, hypertension and other cardiovascular diseases, diabetes, respiratory/pulmonary diseases and cancer (Jordan et al., 2020). In the context of mental health, psychotropic treatments have so far not been shown to be risk factors for SARS-CoV-2 infection.

It is necessary, however, to remember that it is well established in the literature that mental health patients have risk factors associated with the severity of COVID-19 and risk factors linked to mental illness (additive, cognitive-behavioral, and psychosocial vulnerabilities). This situation can complicate both the prognosis of their mental illness and their risk of being infected with the virus (reluctance to adopt preventive practices, in particular) (Javelot et al., 2020).

Given these elements, it should be considered that for adults with mental disorders who do not present risk factors of worse prognosis of infection with SARS-CoV-2, maintaining therapies that provide psychological stability is the primary goal (Javelot et al., 2020).

In the interim, heed should be paid to the dangers associated with precipitous modifications based on arguments unsupported by the best available scientific evidence by patients using psychotropic drugs, such as increased risk of psychic destabilization; risk of secondary accentuation of the use of adjuvant/adjunctive treatments that may have significant adverse effects (anticholinergics, phenothiazine antihistamines, and benzodiazepines); and risk of withdrawal (Wilson & Lader, 2015; Gauthier et al, 2018; Guina & Merrill, 2018; Keks et al., 2019).

In addition, it is known that syndromes caused by discontinuation of psychotropic drugs can be an important risk factor for diagnostic confusion with an initial SARS-CoV-2 infection, in particular including the following symptoms: flu syndrome, headache, fatigue, dyspnea, myalgia, nausea, vomiting, diarrhea, and confusion (Fava et al., 2018). These aspects deserve the utmost caution regarding decisions to cease abrupt changes in pharmacotherapy during the course of the pandemic, by carefully weighing the benefit/risk ratio of the decision.

We stress that the issue of adapting psychopharmacotherapy in this context is still poorly studied (Carvalho, Moreira, de Oliveira, Landim, & Neto, 2020). So far, only the use of clozapine during the SARS-CoV-2 pandemic have been proposed in the international literature (Siskind et al., 2020).

In summary, the recent proposal for a 50% reduction in the dose of clozapine in response to signs suggestive of high effect of clozapine in patients with viral symptoms may be even more warranted since clozapine has recently been defined as the second-generation antipsychotic with the highest risk of inducing pneumonia. Furthermore, it is considered the only

antipsychotic associated with a clear dose-dependent increase in the risk of recurrent pneumonia (de Leon, Norén, & De las Cuevas, 2020).

Despite this information, more studies are needed, and many psychiatrists are already mobilizing to analyze therapeutic adaptations of psychotropic drugs in the context of the pandemic.

4. Final Considerations

The present integrative review confirmed the existence of high prevalence of tobacco consumption in the population, posing serious public health problems. This situation is even more alarming because it involves a portion of the population with higher rates of psychiatric disorders, due to the high dependence on smoking and the various interactions with psychiatric drugs.

These interactions observed in cases of depression and schizophrenia are just a few examples what occurs with comorbidities involving psychiatric disorders and smoking. Through these examples, one can note the importance that smoking plays in the psychological aspects of some pathologies and the harm that smoking causes to patients undergoing drug therapy, including the difficulty of quitting smoking. Thus, there are obstacles to overcome to implement adequate pharmacotherapy, since many drugs in the therapeutic arsenal in these cases have interactions in their metabolism when administered simultaneously with tobacco.

In psychiatric clinical practice, this is of great importance, whether or not the patient is a smoker, because both smoking and abstinence, besides interfering in the patient's mood (a factor that can lead to a poor choice of pharmacotherapy), can also influence the effectiveness of some drugs through the enzyme-inducing effect. In case of the need for abrupt withdrawal of tobacco, the pharmacotherapy must be reviewed regarding the usual doses used, in order to maintain the drugs at adequate levels.

Therefore, due attention should be given to the potential for interaction with smoking, not only in relation to the psychotropic drugs addressed in this study, but also regarding other pharmacological groups that are also influenced by smoking.

Finally, this integrative review contributes to future studies that deepen the consequences of pharmacological interactions between tobacco and psychotropic drugs, with impact on mental health.

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