UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
FACULDADE DE MEDICINA
PROGRAMA DE PÓS-GRADUAÇÃO EM PSIQUIATRIA E CIÊNCIAS DO COMPORTAMENTO

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RELATIONSHIPS AND BENZODIAZEPINE USE DURING THE COVID-19 PANDEMIC

RELACIONAMENTOS E USO DE BENZODIAZEPÍNICOS DURANTE A PANDEMIA COVID-19

Porto Alegre
2022

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Dissertation presented to Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento of Universidade Federal do Rio Grande do Sul in partial fulfillment of the requirements for the degree of Master in Psychiatry.
Advisor: Prof. Dr. Ives Cavalcante Passos

Porto Alegre

2022

CIP - Catalogação na Publicação

de Souza, Fernando Ferreira
Relationships and benzodiazepine use during the COVID-19 pandemic / Fernando Ferreira de Souza. -- 2022.
77 f.
Orientador: Ives Cavalcante Passos.

Dissertação (Mestrado) -- Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento, Porto Alegre, BR-RS, 2022.

1. Benzodiazepínicos. 2. Relacionamentos. 3. Isolamento Social. 4. Distanciamento Social. 5. COVID-19. I. Passos, Ives Cavalcante, orient. II. Título.

Elaborada pelo Sistema de Geração Automática de Ficha Catalográfica da UFRGS com os dados fornecidos pelo(a) autor(a).

RELATIONSHIPS AND BENZODIAZEPINE USE DURING THE COVID-19 PANDEMIC

This dissertation was considered adequate for obtaining the degree of Master in Psychiatry and approved in its final form by the Advisor and the Examination Committee.

Porto Alegre. Approved in: April 22, 2022

The undersigned Examining Committee approves the Dissertation "Relationships and Benzodiazepine Use During The COVID-19 Pandemic", elaborated by Fernando Ferreira de Souza as a partial requirement for obtaining a master's degree in Psychiatry and Behavioral Sciences.

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Advisor: Prof. Dr. Ives Cavalcante Passos – Universidade Federal do Rio Grande do Sul

Dissertation dedicated to Sinval and Sonia Souza.

ACKNOWLEDGEMENTS

Thanks to the following people who helped me in various ways with this project:

Diego Rabelo
Augusto Shintani
Thyago Antonelli
Thiago Roza
Bruno Ramos
Félix Kessler
Keila Ceréser
Gabriel Fries
Daniel Baldez
Nelson Asnis
Alice Cacilhas
Tainara Scalco

* Special thanks to Professor Ives Cavalcante for being my advisor.

“How extraordinary! The richest, longest lived, best protected, most resourceful civilization, with the highest degree of insight into its own technology, is on its way to becoming the most frightened.” (Slovic, 1987. Perception of Risk)

RESUMO

Embora importante no contexto da pandemia COVID-19, o distanciamento social e outras medidas para reduzir a disseminação do COVID-19 também podem estar associados ao sofrimento mental e psicológico, incluindo o uso de benzodiazepínicos (BZD). Essa dissertação se concentra na análise da associação entre qualidade das relações sociais e uso do BZD durante o primeiro ano da pandemia no Brasil. Para isso, realizamos três ondas de uma pesquisa baseada na web (onda 1 [W1]: de 6 de maio a 6 de junho, 2020; onda 2 [W2]: de 6 de junho a 6 de julho de 2020; onda 3 [W3]: de 6 de novembro a 6 de dezembro de 2020) e avaliou se a qualidade das relações e os fatores associados à pandemia COVID-19 (distanciamento social, o número de dias saindo de casa semanalmente, tendo contraído ou em risco para a doença) no W1 foram associados ao uso de BZD em W2 e W3 utilizando regressão logística multinominal. As análises foram ajustadas para potenciais fatores de confusão. Um total de 1.674 participantes (idade mediana de 32,5 anos [IRQ=26 - 41], 86,5% do sexo feminino) responderam ao questionário em W1 e W2 e 1.559 voluntários (idade mediana de 33 anos [IRQ=26 - 42], 83,8% feminino) em W1 e W3. A má qualidade das relações familiares aumentou o risco de uso persistente (aOR 1,97, IC 95% 1,15 - 3,37, p<0,05) e de uso de incidentes de BZD (aOR 2,74, IC 95% 1,19 - 6,27, p<0,05) no período entre o W1 e o W2. Uma má qualidade da relação amorosa em W1 aumentou o risco de uso sustentado de BZD através do W3 (aOR 2,78, IC 95% 1,15 - 6,67, p<0,05). Além disso, ter uma relação amorosa média aumentou o risco de iniciar o uso de BZD durante esse período (aOR 1,56, IC 95% 1,02 - 2,37, p <0,05). A adesão às práticas de distanciamento social não esteve associada a mudanças nos padrões de consumo de BZD. Como tal, chegamos à conclusão de que a qualidade das relações estava consistentemente associada à incidência e persistência do uso do BZD, enquanto outras variáveis, como o distanciamento social, o número de dias saindo de casa/semanalmente, tendo COVID-19 ou correndo risco de doença grave não estavam. Portanto, os médicos devem ser sensíveis à forma como as relações dos pacientes podem afetar o uso de BZD em tempos de dificuldades sociais, como pandemias.

Palavras-chave: Benzodiazepinas; Relações Interpessoais; COVID-19; Isolamento Social; Surtos de doenças

ABSTRACT

Although important in the context of the COVID-19 pandemic, social distancing, and other measures to reduce the spread of COVID-19 may also be associated with mental and psychological distress, including benzodiazepine (BZD) use. This dissertation focuses in analyzing the association between social relationships quality and BZD use during the first year of the pandemic in Brazil. To do so, we conducted three waves of a web-based survey (wave 1 [W1]: from May 6 to June 6, 2020; wave 2 [W2]: from June 6th to July 6th, 2020; wave 3 [W3]: from November 6th to December 6th, 2020) and assessed whether relationships quality and factors associated with the COVID-19 pandemic (social distancing, the number of days leaving home weekly, having contracted or being at risk for the disease) at W1 were associated with BZD use at W2 and W3 using multinomial logistic regression. The analyses were adjusted for potential confounders. A total of 1,674 participants (median age 32.5 years [IRQ=26 - 41], 86.5% female) answered the questionnaire in W1 and W2 and 1,559 volunteers (median age 33 years [IRQ=26 - 42], 83.8% female) in W1 and W3. Poor quality of family relationships increased the risk of persistent use (aOR 1.97, 95% CI 1.15 - 3.37, $p<0.05$) and of incident use of BZD (aOR 2.74, 95% CI 1.19 - 6.27, $p<0.05$) in the period between the W1 and W2. A poor quality of loving relationship in W1 increased the risk of sustained BZD use through W3 (aOR 2.78, 95% CI 1.15 - 6.67, $p<0.05$). Furthermore, having an average loving relationship increased the risk of starting BZD use during this period (aOR 1.56, 95% CI 1.02 - 2.37, $p <0.05$). Adherence to social distancing practices was not associated with changes in BZD consumption patterns. As such, we concluded that the quality of one's relationships was consistently associated with BZD use incidence and persistence, while other variables, such as social distancing, the number of days leaving home/weekly, having COVID-19 or being at risk for severe disease were not. Therefore, clinicians should be sensitive to how patients' relationships may affect BZD use during times of social hardship such as pandemics.

Keywords: Benzodiazepines; Interpersonal Relations; COVID-19; Social Isolation; Disease Outbreaks

LIST OF ACRONYMS

aOR	Adjusted odds ratio
BNADS	Brazilian National Alcohol and Drugs Survey
CAAE	Certificado de Apresentação para Apreciação Ética
CEP	Comitê de Ética em Pesquisa
CI	Confidence interval
CDC	Centers for Disease Control and Prevention
CONEP	Comissão Nacional de Ética em Pesquisa
COVID-19	Coronavirus Disease 2019
CVV	Centro de Valorização da Vida
ELSA	Estudo Longitudinal de Saúde do Adulto
GAD-7	Generalized Anxiety Disorder-7
HCPA	Hospital de Clínicas de Porto Alegre
HIV	Human immunodeficiency virus
IRQ	Interquartile range
MERS	Middle East respiratory syndrome
NESDA	Netherlands Study of Depression and Anxiety
NSDUH	National Survey on Drug Use and Health
PHQ-9	Patient Health Questionnaire-9
PTSD	Post-traumatic stress disorder
R-UCLA	Revised UCLA Loneliness Scale
SARS	Severe acute respiratory syndrome
W	Wave
WHO	World Health Organization

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SUMMARY

1. PRESENTATION

The current work consists of the master's dissertation entitled "Relationships and benzodiazepine use during the COVID-19 pandemic", presented to the Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento da Universidade Federal do Rio Grande do Sul.

The work described will be presented as follows:

- Introduction, literature review, study objectives, and ethical considerations.
- Research paper manuscript submitted for publication with its associated figures, tables, and references.
- Conclusions and final considerations.
- Research supplementary materials.

2. INTRODUCTION

The first case of the novel coronavirus disease (COVID-19) was reported in Wuhan, China in December 2019 (1). Since then, it has spread to every country in the world, with more than 250 million reported cases and 5 million confirmed deaths as of February 2022 (2). In Brazil, the first confirmed case was dated February 26, 2020. In March 2020, the World Health Organization officially classified the spread of the virus as a global pandemic (3). In the absence of effective means to treat or prevent the disease, unprecedented sanitary control measures have been promoted around the world, including in Brazil (4). These measures include social distancing, quarantines, school closures, lockdowns, and bans on public gatherings (2,5).

The unique situation created by the COVID-19 pandemic in terms of social isolation, physical distancing and prolonged lockdown has raised concerns about its impact on mental health and substance use (6–8). Suddenly, people worldwide had to deal with different potentially serious psychosocial stressors at the same time. When people experience distressing or threatening events, they often turn to loved ones for comfort, help, and support. Psychological theories about interpersonal relationships and attachment underscore the importance of one's own relationships in mental illness, substance use and mental health (9–16). Prospective studies have shown an increased risk of death in people with a low quantity and a low quality of social relationships (17). Relationship quality and stability have also been associated with better overall health, and social support is particularly important during times of stress (18–20). Likewise, relationship satisfaction and stability are positively associated with viewing partners as sources of support (18,21).

Benzodiazepines are commonly prescribed to treat many psychiatric disorders (22). Although not suitable for long-term treatment, its pharmacological properties allow it to be used in acute situations when immediate symptom control is desired. Nonetheless, it has long been known that benzodiazepine use (particularly with prolonged use) is associated with important side effects, including cognitive decline, daytime sleepiness, traffic accidents, dependence and withdrawal syndrome (23,24). However, benzodiazepines are commonly prescribed and abused (25). Varied trends in benzodiazepine prescription and use have been reported during the pandemic, with benzodiazepine dispensing in the United States increasing significantly in the first year of the outbreak (26,27).

Many of the changes brought about by the COVID-19 pandemic have influenced factors known to be associated with benzodiazepine use, abuse, and abuse (e.g., social support)

(22,25,28). In this way, it is important to examine and delineate the interaction between relationship quality and compliance with social distancing measures implemented at the onset of the COVID-19 pandemic and its impact on mental health and benzodiazepine use over. We hypothesized that compliance with social distancing measures would affect benzodiazepine use. We also assumed that relationships quality at the start of social distancing measures would influence the use of such drugs in the months that followed.

3. LITERATURE REVIEW

3.1 Benzodiazepines

Benzodiazepines are a class of drugs typically used to treat anxiety and insomnia but are also indicated for the treatment of panic disorder, manic and psychotic states, status epilepticus, some pain syndromes, and as preanesthetic drugs (29). Ideally, these drugs should only be used for short periods of time, as they have short- and long-term side effects such as sedation, confusion, cognitive effects, and the potential for addiction (24). Studies have also shown that a large proportion of benzodiazepine users consume them for long periods of time, sometimes over a year (22).

Nonetheless, these drugs are also commonly prescribed and used. American data from the 2020 National Survey on Drug Use and Health (NSDUH) shows that about 6 million American citizens aged 12 and over (about 2.2% of the population) abused tranquilizers in the previous year, including about 5 million specifically benzodiazepine drugs, making tranquilizers the third most abused illicit substance in the United States (30). Studies of people with depression or anxiety disorder show prevalence estimates of up to 15%, according to data from the Netherlands Study of Depression and Anxiety (NESDA) (31).

The risk factors for benzodiazepine abuse and the demographics of this population show striking differences from other substance abuse populations. The role of gender is not well understood, as it varies across several studies (32,33), and young adults between the ages of 18 and 35 make up the majority of abusers (28,30,34). Long-term use of benzodiazepines can lead to physical dependence, with many long-term benzodiazepine users experiencing a withdrawal syndrome after stopping the drug. Also, long-term use does not equate to addiction. Data from a Japanese cohort designed to examine the rate at which new benzodiazepine users became chronic users analyzed data from 84,412 patients with new benzodiazepine prescriptions. Among them, 35.8% continued use for three months, 15.2% for one year, and 4.9% for eight years without ever not using for at least three months. Predictors for long-term use in the study were older age, psychiatrist prescription, regular use, high dosage, and concomitant prescription of other psychotropic drugs (35). Benzodiazepine use, abuse and misuse are strongly associated with comorbid psychiatric disorders and personal or family history of substance use disorders (33,36,37). Psychiatric comorbidity is higher in benzodiazepine abusers than in other substance abuse populations, reaching around 40% in the 2020 NSDUH (30).

Data on benzodiazepine use in Brazil are mainly derived from convenience (e.g., elderly) or from small samples (29,38), which skews overall estimates of use of these drugs. Larger studies with a more representative sample include data from the Brazil Longitudinal Health Study (ELSA-Brazil), a cohort of state officials from six different sites in Brazil with 15,105 participants, showing current benzodiazepine use among participants of 3.88%. The number was even higher for those with major depression (13.9%), generalized anxiety disorder (9.5%), or those with any mental disorder (7.8%). The study also reported a direct association between benzodiazepine use and a psychiatric diagnosis, clinical comorbidities, chronic insomnia, older age, and living alone (39). The second Brazilian National Alcohol and Drugs Survey (II BNADS), conducted between November 2011 and March 2012, surveyed 4,607 Brazilians aged 14 and over from all regions. The nationwide lifetime and 12-month prevalence of benzodiazepine use were 9.8% and 6.1%, respectively. Females showed higher rates than males for lifetime use (13.2 vs. 6%) and last year use (8.6% vs. 3.4%), respectively; the 12-month prevalence reached almost 15% in divorced/separated women and 4–12% in women aged 40 to 59 years. Urban populations and the South and Midwest regions had the highest consumption rates in the previous year. Sociodemographic factors associated with prior year use were female gender and older age (40).

3.2 Pandemics impact on mental health:

Outbreaks of infectious diseases affect not only the physical but also the mental health of those infected and those around them. Maunder et al. (2003) reported results of a study at a Toronto hospital during the 2003 severe acute respiratory syndrome (SARS) outbreak. Patients hospitalized with SARS reported anxiety, loneliness, boredom, and anger, and worried about the effects of quarantine and contagion on family members and friends. The broader inpatient hospital system was also affected, requiring quarantine upon discharge, or delaying it. However, patients without SARS were also excluded from family visits for risk of contamination and demonstrated their distress. They also reported insomnia, anxiety, and had interpersonal arguments with hospital staff (41).

Salehi et al., 2021, estimated an overall prevalence rate of 18% for symptoms related to post-traumatic stress disorder (PTSD) in a meta-analysis of 38 studies and a total of 19,428 people from 8 countries conducted in previous coronavirus outbreaks (42). Ahmed et al., 2020, reviewed data from 28 studies on patients hospitalized or placed in an intensive care unit (ICU) for SARS or Middle East respiratory syndrome (MERS). Their analysis showed that about one-third of SARS and MERS survivors had mental illnesses lasting longer than 6 months,

including PTSD, depression, and anxiety. These estimates are much higher than the prevalence of these disorders in other ICU patients (43). This indicates that these long-lasting mental health effects are not only related to the severity of the illness, but also to associated factors such as fear (44), stigma (45), difficulties in complying with quarantine (46), and the psychological impact of the quarantine experience (47). The importance of the stigma associated with viral infections is also supported by Tedstone and Tarrier, 2003. They systematically examined the occurrence of PTSD in adults with several diseases, from clinical medicine, infectiology, obstetrics and surgery. The highest prevalence rates were identified in patients treated in intensive care units who were infected with human immunodeficiency virus (HIV). Existing patient characteristics may predispose individuals to developing PTSD, but such studies indicate that so do other factors such as social support and negative interactions with health care workers. The severity of the physical illness itself is also not predictive of PTSD (48).

Coronaviruses are also known to be associated with neuropsychiatric conditions, both in the acute disease and after it (49). Post-infectious sequelae of viral infection often include damage to many different organs through a variety of pathological mechanisms, with the brain being one of the organs most often targeted. A review of SARS and MERS survivors reported multiple long-lasting clinical complications affecting various aspects of health, including chronic fatigue, decreased exercise capacity, muscle weakness, increased depression, anxiety, PTSD, and sleep disorders.

An overall decline in quality of life was observed for up to 1 year after major coronavirus outbreaks (47). The same seems to be the case in this pandemic. A meta-analysis of the prevalence of mental disorders using 27 studies sampled 9,605 patients who had recovered from COVID-19. As in previous outbreaks, high rates of PTSD, anxiety, mental distress, depression, and sleep disorders were reported (50).

This has sparked interest in the effect the pandemic will have in psychiatric medication use, specially in those with abuse potential and dependence risk as benzodiazepines and opioids (51). The number of benzodiazepine prescriptions in the United States the last two decades have been on the rise. A cross-sectional study with data from 2003 through 2015 showed that in outpatient settings benzodiazepine prescriptions increased from 3.8% to 7.4%. Primary care accounted for about half of all benzodiazepine prescriptions (52). Growing rates of overdose deaths involving benzodiazepines have also been reported before and during the COVID-19 pandemic in that country (53,54).

3.3 Social relationships

Existing research on the effect of major external stressors on couple relationships has relied on couples recruited and studied after experiencing a crisis and has come to conflicting conclusions about whether the effects are positive or negative (55–57). Although these studies offer limited opportunities to examine changes in relationship outcomes, they suggest that crises can have variable rather than uniform effects on relationships.

However, multiple studies show that people who face stress from outside of the relationship, such as financial or work stress, are more likely to interact with their partner in ways that affect relationship quality over time, such as being overly critical, blaming, or being unresponsive to their partners (58,59). Increased stress can also affect the perception of a partner's need for support and thus the ability to offer it in stressful situations (60). Leach et al, 2013, examined data from a longitudinal community survey that assessed the health and well-being of 3,820 Australians. Their results showed that relationship status and mental health associations were moderated by relationship quality in both men and women. For women, a poor-quality relationship was associated with higher levels of anxiety than being single (61).

Although the precise impact of the COVID-19 pandemic on relationships has yet to be better understood, several efforts have been directed toward it.

Pieh et al., 2020 assessed differences in several mental health and well-being measures with relationship quality during the COVID-19 pandemic lockdowns. They reported that people in poor relationships were more than three times as likely to score positively on both the PHQ-9 depression scale and the GAD-7 anxiety scale as compared to people with good relationship quality. Relationships per se weren't associated with better mental health, but relationship quality was (62).

Juvonen et al., 2022, using data from young adults, showed that greater number of friends over time and greater satisfaction with electronic interactions with friends during the pandemic were associated with lower social and general anxiety and depressive symptoms. Loneliness was protected by higher quality friendships, greater contact with friends, and more frequent and satisfying electronic communication with friends (63).

Philpot et al. compared social relationships data from February 2018 to a time when social distancing measures were in place, May 2020. Their analysis showed that individuals experienced increased feelings of emotional support, instrumental support, and loneliness and decreased feelings of friendship and perceived hostility when social distancing. The study also

showed that those with low self-reported health reported lower feelings of emotional support and that women experienced increased feelings of loneliness during lockdowns (64).

Moak and Agrawal, 2010, reviewed the results of the National Epidemiological Survey on Alcohol and Related Conditions, which surveyed 34,653 adults at two different times between 2001 and 2005. Their study shows that low perceived social support is correlated with an increased prevalence of major depressive disorder, generalized anxiety, social phobia, and multiple physical health problems. At the same time, they reported a strong association between excellent self-perceived physical health and high levels of social support (65).

However, dependency on partners has increased further during the COVID-19 pandemic. People around the world were isolated at home with their families for weeks: adults worked from home or were laid off, children did not go to school, and physical contact with people outside of one's household (including other family members) was discouraged or banned. This context raised questions on the impact of the pandemic on relationships between individuals and its implications for mental health.

4. EXPLANATORY STATEMENT

The COVID-19 pandemic has created a new social environment as physical distancing is required to contain the transmission of the outbreak. However, such changes in social interactions may be associated with benzodiazepine use. Benzodiazepines are widely used, but the negative consequences associated with their use can be prevented. Studies are needed to understand the factors associated with changes in benzodiazepine use patterns, particularly during moments of social distress, so that effective preventive measures can be taken.

5. OBJECTIVES

5.1 General objective

- Identify possible factors related to the use of benzodiazepines in the Brazilian population during the first year of the COVID-19 pandemic.

5.2 Specific objectives

- Analyze whether the quality of interpersonal relationships (family, friends and romance) and COVID-19-related factors (family, friends or self-diagnosis of COVID-19, virus exposure, belonging to a high risk group for serious illness, adherence to social distancing measures, and days leaving home weekly) in the May-June 2020 are associated with changes in the pattern of benzodiazepine use (incidence, remission, persistence, or non-use) in one (June-July 2020) and six (November December 2020) months of follow-up. If so, examine if this association persists after controlling for known factors associated with benzodiazepine use in our population (age, Brazilian region, sex, skin color, household income, education level, sleep quality, suicidal ideation, psychiatric history, depressive symptoms, anxiety symptoms and loneliness).

- Analyze whether sociodemographic characteristics, lifestyle behaviors and mental health factors would be associated with changes in benzodiazepine use over the same period.

6. ETHICAL CONSIDERATIONS

Data collection was initiated after approval of the project by the Comitê de Ética em Pesquisa (CEP) of the Hospital de Clínicas de Porto Alegre (HCPA) and by the Comissão Nacional de Ética em Pesquisa (CONEP) via Plataforma Brazil (CAAE: 30222820.4.0000.5327). Informed consent was given electronically before initiating the first wave questionnaire. Participants were advised that anonymity would be guaranteed during the first wave of the study, that collected data would only be analyzed as part of the study dataset (not individually), and that the project had been approved by the ethics committee of the HCPA and by the CONEP.

The first wave of the study was based on snowball sampling and was advertised on different social media vehicles (e.g., Instagram, WhatsApp) and any interested adult could participate by answering the questionnaires and by sharing the research group social media posts informing about the survey. Participation in further assessments were proposed for those who completed the first questionnaire and were willing to associate their e-mail address with the research group so that they could be contacted again in one and six months for follow-up.

As the questionnaires touched sensitive topics such as mental health and pandemic related issues, before starting the questionnaire, information and advising about potential risks associated with answering about such topics. Orientation was given about possible negative emotional reactions when being asked about personal feelings and attitudes in a stressful moment. In addition, filling out the questionnaires could generate tiredness, annoyance, or embarrassment. Participants were also reiterated that at any time they could withdrawal from the study if they felt so. If, when answering the survey, the participant needed psychological help, a telephone number and an e-mail contact was presented for assistance by one of the researchers or through the Centro de Valorização da Vida (CVV).

7. PAPER

Following is the manuscript submitted for publication in the Brazilian Journal of Psychiatry.

8. CONCLUSION

Bowlby, 1973, observed that family members stay in proximity for days or weeks after a disaster because the affiliation is comforting during a crisis (66). In the case of the COVID-19 pandemic, however, proximity to family members was not always a choice. The way the pandemic brought changes to normal social interactions, work, leisure, education, and society underscored the importance of how people live and interact with each other. It has been known that poor social interactions could lead to different forms of physical and mental issues. It is in this context that the present dissertation aimed in analyzing the impact of the COVID-19 disease and its containment measures, along with the quality of individuals relationships at the first moments of the pandemic in Brazil would influence the use of sedatives and tranquilizers further into that year.

The longitudinal design of the study with follow-up assessments at one and six months allowed us to investigate predicting factors and their persistence or not in that period. Also, our sample included individuals from all Brazilian states, with enough size to make possible the examination of a wide range of possible confounding factors. Also, to the best of our knowledge, it is the only study to focus specifically on this interaction.

Besides that, the findings are not easy to generalize. Several concerns have been raised about mental health surveys during the COVID-19 pandemic. Convenience selection of internet surveys restricts the representativeness of the sample. More interestingly, survival-bias on surveys respondents is being discussed as a defining issue on the reliability of such results for broader applications (67–69). Still, the study points to a topic that could be of interest in understanding in a society that seems to be, at least to some degree, integrating to its normal functioning some of the ways individuals interacted during the first year of the pandemic.

As the COVID-19 pandemic seems to be subsiding, more research is needed to understand its momentaneous as well as its possibly sustained impacts on substance use, interpersonal relationships, and mental health. The extent to which the pandemic will have changed the ways people interact with each other is still to be defined.

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10. SUPPLEMENTARY MATERIAL