The Impact of COVID-19 on Prescription Psychotropic Drug Dispensing and Consumption: A 1-year Systematic Review and Meta-analysis

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Abstract

The coronavirus (COVID-19) pandemic has been associated with adverse psychological symptoms. Psychotropic prescription drugs are a critical tool in treating and controlling a variety of psychopathological conditions, which raises concern in terms of potential overuse and irrational use. Available data regarding the use and prescribing practices of psychotropic prescription drugs during the COVID-19 pandemic are inconsistent. Therefore, a systematic review and meta-analysis was conducted with the aim of investigating the change in psychotropic prescription drug use and dispensing in relation to COVID-19. Pub-med and Web of Science Databases were systematically searched, and a total of 30 studies were included (23 prevalence estimates, and 19 correlation coefficient estimates; total N = 5,133,032). The yielded findings demonstrated a statistically significant increase of 16.34% (95% Confidence Interval [CI]: 9.11 to 23.57) in prevalence estimates of psychotropic prescription drug use. Furthermore, the conducted meta-analysis yielded a small positive statistically significant correlation r = 0.11 (95% CI: 0.05 to 0.16), implying a small increase in psychotropic prescription drug use and dispensing pre relative to post COVID-19. The association between COVID-19 and adverse mental health, as well as the increased use of psychotropic medications, may lead to an upsurge in substance use related disorders and overdose-related deaths. This is important to know, given that many substance use treatment programs during the pandemic have been disrupted. It may be essential for policy makers and health officials to address mental and behavioral health through telemedicine.

Keywords: COVID-19, psychotropic prescription drugs, psychopharmacology, prescribing, dispensing, systematic review, meta-analysis

The Impact of COVID-19 on Prescription Psychotropic Drug Dispensing and Consumption: a 1-year Meta-analysis

The coronavirus (COVID-19) pandemic has devastated many countries around the world leading to far-reaching transformations in society. As the number of COVID-19 cases around the world began to rise, and the death toll surged, governments of many countries implemented public health measures in hopes of reducing the spread of the COVID-19 virus. Such public health measures include lockdowns, social distancing, and self-isolation (Kwong et al., 2020). Despite the fact that such measures are crucial for reducing the number of infected people, they may also have a substantial impact on one's mental health and well-being (Kwong et al., 2020). Previous research suggests that the most common ramifications of past pandemics and natural disasters are anxiety, fear, insomnia, depression, somatic symptoms, stigmatization, and abandonment (Jarego et al., 2021). For example, during the 2015 outbreak of the Middle Eastern Respiratory Syndrome (MERS) in Korea, 80.2% of the general public reported fear of becoming infected, 47.2% of MERS patients reported experiencing symptoms of anxiety in isolation, while 19.4% reported protracted anxiety symptoms which continued up to 6 months after the outbreak (Jeong et al., 2016; Esterwood & Saeed, 2020). Similarly, during the 2014 Ebola outbreak, exacerbated anxiety levels among the American population were reported, due to widespread media coverage concerning only a handful of cases (Morganstein & Ursano, 2020). This signifies the possible mental health effects that public health measures can have on individuals during the pandemic.

Impact on Mental Health and Pre-existing Mental illness

Recent research reveals a clear correlation between the present pandemic and negative psychological symptoms, such as anxiety and depression, causing some to expect a second pandemic of mental health issues in the future (Choi et al., 2020; Rajkumar, 2020). Supporting this statement, current studies in relation to the COVID-19 pandemic have shown an upturn in anxiety and insomnia in both healthcare workers, and the general population (Lai et al., 2020; Pappa et al., 2020). According to the American Psychiatric Association (2020), about 36% of people reported effects of the pandemic on their psychological well-being, 48% of the general population started experiencing anxiety, and 19% reported insomnia (Agrawal, 2020; Lai et al., 2020; Pappa et al., 2020). Moreover, a study examining symptoms of depression among the

general population in China during the early months of the pandemic found that 28.9% of individuals reported moderate to severe depression (Wang et al., 2020). Somewhat higher rates were described in a study conducted in February 2020 (Huang & Zhao, 2020). A study conducted in May 2020 found that over half of its sample (65.7%) reported clinical levels of depression (Fitzpatrick et al., 2020). Not only does this signify the potential effects of the pandemic on the mental health of individuals, but it may also suggest a worsening of mental health as the pandemic progresses (Kozloff et al., 2020).

Furthermore, those with pre-existing mental illness, may be at even greater risk, especially those with more severe mental illnesses (i.e., schizophrenia, and bipolar disorders; (Kozloff et al., 2020; North et al., 2009; Stefana et al., 2020). Stress, social isolation, and delays in treatment availability due to the pandemic, may aggravate symptoms in those with severe mental illness, who are especially prone to isolation and loneliness (Chatterjee et al., 2020; Hamada & Fan, 2020). A study investigating present symptoms of stress, depression, and anxiety reported significantly higher levels among patients with pre-existing and severe mental illness (i.e., major depressive disorder, bipolar disorder, psychotic disorders) compared to mentally healthy controls (González-Blanco et al., 2020; Van Rheenen et al., 2020). Similarly, a study by Muruganandam et al. (2020) which examined the impact of COVID-19 on individuals with severe mental illness, revealed that about one third reported relapse in psychiatric symptoms. The uncertainty regarding the development of the pandemic, the restrictions set forth by many governments (e.g., lockdowns, curfews, social distancing), as well as financial, economic, and social consequences poses a great risk not only to the psychological wellbeing of individuals, and their ability to cope with stressors, but also to the use, misuse, and abuse of substances (Cao et al., 2020; Jarego et al., 2021; Mazza et al., 2020; Moccia et al., 2020; Pappa et al., 2020; Park et al., 2020; Wang et al., 2020; Xiao, 2020).

Stress, Social Isolation, and Self-Medicating

Considering the importance of social interaction and its function as an effective reinforcer for humans, an absence of it may lead to various complications (Koob et al., 2021). In the current circumstances, given that adaptive coping mechanisms such as social support and other active coping strategies may not be manageable due to restrictions, many may turn to other forms of coping (Jarego et al., 2021). For example, social isolation could serve as a source of stress which

may lead to maladaptive coping strategies such as self-medicating. Prolonged social isolation in and of itself has been associated with an increased risk of drug use (Eitan et al., 2017). Several studies have demonstrated a link between stressors such as social isolation, unemployment, and loneliness and increases in antidepressant and antianxiety drug use (Colman et al., 2008; Sihvo et al., 2008).

The Self-Medication Hypothesis (SMH) suggested by Khantzian (1997) has two key premises: psychoactive substances alleviate psychological distress, and personal choice for a specific substance is contingent on its psychopharmacological qualities. During or following a natural disaster the use of substances to cope with stress exposure can be regarded as self-medication (Alexander & Ward, 2018). For individuals who suffer from a history of drug abuse or mental health difficulties, drug use may be a natural or salient response to stress, whereas the opposite may be true for those who are mentally well (Abrams et al., 2002; Alexander & Ward, 2018; Gordh et al., 2011). Moreover, in the lack of effective coping techniques, self-medication may be influenced by an individuals perceived coping self-efficacy — "Perceptions of the ability to cope with the physical, cognitive, and emotional demands of stressors" (Sandler et al., 2000) — which may determine if the behavior is begun and/or sustained after experiencing stress (Alexander and Ward, 2018; Cinciripini et al., 2003; Engels et al., 2005; Skutle, 1999). In the conceptual model put forth by Alexander and Ward (2018), 'self-efficacy', 'mental suffering', and 'perceptions of self-medication', mediate the effect of adversity exposure on drug use" (p.181). Thus, exposure to a disaster lowers self-efficacy, resulting in increased psychological stress, and thereupon increased self-medication, which ultimately leads to an increase in post-disaster drug use (Alexander and Ward, 2018).

Trends in psychotropic drug use and prescribing practices

Given the prevalence and significance of mental disorders during the COVID-19 pandemic, psychotropic prescription drugs are a critical tool in treating and controlling a variety of psychopathological conditions (Sadock et al., 2016), which raises concern in terms of potential overuse and irrational use (Estancial Fernandes et al., 2018). As stated by the Center for Disease Control and Prevention (CDC), to cope with stressors related to COVID-19, an increase in the use of substances was reported among 13% of the American population (Czeisler et al., 2020). Likewise, self-reports from 12 different countries revealed a worsening of pre-existing

mental illness in two-thirds of patients, which demanded beginning psychotropic medication, or change in dose (Gobbi et al., 2020). Furthermore, according to statistics provided by the European Monitoring Centre for Drugs and Drug Addiction (2020) [EMCDDA], there has been a shift in consumption of illegal to legal substances during the period of confinement, specifically an increase in the frequency and amount of prescription drug use. Several studies, amongst which a study by Gili et al. (2021) found an overall increase in the consumption of benzodiazepines during the COVID-19 lockdown as well as after the lockdown. In addition, recent data suggests an increase in drug overdoses during the time frame in which public health measures were implemented (Alter & Yeager, 2020). Likewise, a study examining trends in prescription drug use and prescribing practices between January 19, 2020, and March 15, 2020, reported an increase in claims of antidepressants, and central nervous system (CNS) depressants (i.e., anxiolytic, hypnotic, and sedative medications; (Scripts, 2020). Many experts substantiate this as a result of individuals struggling with depression and anxiety due to COVID-19 confinement measures (EMCCDA, 2020). However, available data regarding the use and prescribing practices of psychotropic prescription drugs during the COVID-19 pandemic are contradictory and appear to be different at national levels. For example, several studies suggest a reduction in psychotropic drug consumption and prescribing practices during the period of 2020 compared to the same period in 2019 (Di Lorenzo et al., 2021; Sklar et al., 2020). This reduction has been described as a consequence of the increased number of tele-consultations which did not authorize the delivery of pharmacotherapy (Di Lorenzo et al., 2021; Sklar et al., 2020). However, the opposite can be observed in the United States of America (U.S.), where many scholars and policymakers promoted laxed restrictions for controlled substances, resulting in increased compensation for e-health services; increased accessibility to take-home doses of buprenorphine and methadone, and other medications for opioid use disorder (MOUD; (Dunlop et al., 2020; Marsden et al., 2021). Although, even in this case findings are mixed, with some studies reporting significant decreases in the number of prescribers and patients writing and filling opioid and benzodiazepine prescriptions, respectively (Downs et al., 2021). As such, changes in psychotropic prescription drug use reported among several studies are not in parallel, suggesting probable heterogeneity between studies. This signifies the importance of conducting further research, to obtain a better understanding of between-study heterogeneity, by identifying sources of variation (e.g., type of drug, age, and gender distribution).

Given the current circumstances of the pandemic, limitations to treatment access, resources, and social support are evident (Boden et al., 2021). A recent report published by the World Health Organization (2020) [WHO] (2020) found that over 60% of the 130 countries assessed, reported a reduction in mental healthcare for marginalized populations, 49%-67% reported interruptions in psychological services (i.e., counseling and psychotherapy), and 30% reported interruptions in visits for the treatment of addictive and substance abuse-related disorders. Although, psychotherapy is the protocol treatment for many mental health issues such as anxiety and insomnia (Agrawal, 2020), it might be compelling for healthcare providers to opt for pharmacological treatment rather than psychotherapy during the pandemic, as it can be seen as a "quick fix" (Argawal, 2020, p. 15). On this basis, one might expect a change in the use of psychotropic prescription drugs, as well as in psychotropic prescribing practices.

Research objective & Implications

Given the rising concern regarding the risks and safety of psychotropic prescription medications, overdose related deaths, addictions, and prolonged withdrawal syndromes (Agrawal, 2020), as well as the mental health crisis expected to be caused by the COVID-19 pandemic, it may be beneficial to understand the use and prescribing practices of different psychotropic drugs during the COVID-19 pandemic relative to pre-pandemic times. It would be essential to investigate if patients with pre-existing mental illness who use psychotropic prescription medications also have increased substance use during the pandemic, as these patients are often ostracized, and maybe at far greater risk for worsening of psychiatric illness, engaging in suicidal thoughts, developing substance use disorders (SUD) and/ or contracting COVID-19 (Gunnell et al., 2020; Płomecka et al., 2020; Yao et al., 2020). Furthermore, there is a need for studies to review fewer common forms of substance use variants to better understand how the COVID-19 pandemic is impacting vulnerable populations (Kumar et al., 2021). Addressing substance use in at risk populations (e.g., people with pre-existing mental illness, frontline workers) can help mitigate exacerbation of mental illness, reduce suicidal ideation, and aid in alleviating long-term morbidity and mortality caused by the pandemic (Gobbi et al., 2020).

Despite overlapping findings with regard to prescribing practices and consumption of psychotropic drugs during the COVID-19 pandemic and initial studies suggesting an increase in both, the overall prevalence of prescribing practices and consumption rates of prescription

opioids, benzodiazepines, z-drugs, as well as antidepressants has not been subjected to systematic review and meta-analysis. Given the growing number of studies addressing substance use in relation to COVID-19 published in the last year, we planned to conduct a systematic review and meta-analysis of all available studies, investigating change in psychotropic prescription drug use in the general and clinical population during the COVID-19 outbreak, as well as potential sources of heterogeneity. On this basis, the following hypothesis has been derived: COVID-19 will be related to increased psychotropic prescription drug use (i.e., antidepressants, benzodiazepines, z-drugs, prescription opioids etc.) and prescribing practices.

Methods

Design

This study is a systematic review and meta-analysis of cross-sectional, retrospective, observational, descriptive, and time-series studies examining the change in use of psychotropic pre-scription drugs during the COVID-19 pandemic relative to pre-covid. This study was conducted in accordance with the PRISMA guidelines (Moher et al., 2010) for reporting systematic reviews and meta-analysis.

Procedure

An a priori review protocol was made, defining objectives, search and selection strategy, eligibility criteria, and methodological quality assessment.

Eligibility criteria

Articles were included if they: (1) reported data on the change in substance use during the COVID-19 outbreak relative to pre-pandemic in either the general, or clinical population; (2) if the data necessary for statistical calculations was reported in the article or was available via the corresponding authors; (3) was written in the English, Dutch, French, German, Arabic, Spanish, Greek, or Turkish language; and (4) they reported original data (i.e., reviews, commentaries, editorials, and meta-analyses were not included).

Search and Selection Strategy

A literature search was conducted using the PubMed Database and Web of Science databases. The following keywords were used: (COVID-19) AND (prescription drug OR benzodiazepines OR psychoactive OR psychotropic OR psychopharmacology OR psychiatric

medication OR anticonvulsant OR antidepressant OR antipsychotic OR anxiolytic OR recreational drug OR stimulant medication OR self-medication OR mental health drug OR anti-anxiety medication* OR sleep aid OR "alcohol-related disorders" OR alcohol OR prescription drug OR substance use OR substance misuse OR substance abuse OR opioid OR Opiate OR heroin OR Opium OR sedatives OR tranquilizers OR major tranquilizers OR amphetamine). The full search strings per database will be provided in an Appendix or upon request. No grey literature search was performed. All databases were searched for studies published between January 2020 through July 1, 2021. The final search date was July 1, 2021. A first decision on eligibility was based on the title and abstract of the resultant articles. A second decision was based on screening of the article's full text. All five members of the research project made a final decision on the eligibility of each article, based on the aforementioned inclusion and exclusion criteria.

Measures

The study's main outcome was any change in use, dispensing, and filling of prescription psychotropic drugs related to COVID-19 (comparison pre-covid & post-covid). The exploratory outcomes were changes in specific types of prescription psychotropic drug use, as well as potential sources of heterogeneity. In the present meta-analysis, the following classes of psychotropic prescription drugs were included: central nervous system (CNS) depressants, prescription opioids, antipsychotics, and antidepressants. CNS depressants consist of medications which are commonly used in the treatment of anxiety, panic attacks, acute stress, and insomnia (Gunja, 2013). This group of medications includes sedatives and hypnotics such as benzodiazepines (i.e., diazepam, alprazolam, clonazepam etc.), and non-benzodiazepine sleep medications (Z-drugs; i.e., zaleplon, eszopiclone, zolpidem etc.; Gunja, 2013). The opioid class of drugs includes natural, semi-synthetic, and synthetic opioids. For the purpose of this meta-analysis, only prescription opioids were included (i.e., morphine, prescription fentanyl, methadone, buprenorphine, etc.). The types of antidepressants covered in this meta-analysis were selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs). All outcomes were measured through self-reports, interviews, observations, hospital data, pharmacy data, (online) surveys, and laboratory analysis (i.e., blood, urine, and hair).

Risk of Bias and Quality Assessment

The method suggested by Livense et al. (2020) was used to evaluate maintained articles with respect to the methodological quality and risk of bias. The inclusion of articles was not decided upon quality assessment.

Data extraction

A pre-designed data extraction form was used to extract information on the following variables: sample size; instruments used to assess substance use; design; average age; gender distribution as percentage of females; population; continent; and prescription psychotropic drug use.

Statistical analyses

All analyses were conducted using the modules for meta-analysis available in JAMOVI, (2021) version 1.8.

The primary outcome of the meta-analysis was a change in use, dispensing, and filling of psychotropic prescription drugs. Two separate analyses were conducted. In the first analysis, studies which assessed a change in psychotropic drug use during COVID-19 were considered. The associated data for the mentioned analysis were entered as proportions along with their respective sample size. In the second analysis, the comparison between pre COVID-19 and post COVID-19 psychotropic drug use was assessed. Therefore, correlation coefficient (r), and sample size were calculated from each study. The correlation coefficient *r* was converted into the Fisher's z scale to perform analyses and converted back to *r* correlations for reporting. Only studies comparing psychotropic drug use (i.e., period A compared to period B) were entered in this analysis. The change in psychotropic drug use was reported separately for each analysis. Data were pooled in all analyses and an overall effect size, and 95% CI were reported. Furthermore, separate analyses were run for any kind of psychotropic drug use, as well as the specific classes of psychotropic drug use (i.e., CNS depressants, prescription opiates, antipsychotics, and antidepressants).

It should be noted that negative correlations and a negative relative use of psychotropic prescription drugs indicate a decrease.

To assess between study heterogeneity, the *Q* statistic was used. By testing the null hypothesis, it was assured that the individual study effect sizes were similar enough, so that a common population effect size was computed. Furthermore, the I^2 statistic was calculated to explain the amount of variation among the studies due to heterogeneity. According to Higgins and Thompson (2002), no identified heterogeneity is demonstrated by a value of 0%, while a value of 25% indicates low, 50% moderate, and 75% high heterogeneity. If heterogeneity was evident, moderator analyses were carried out to explore how certain attributes (i.e., average age, gender distribution, measures used, study design, continent, medical and non-medical use, and population) affect variation in outcome. An inspection of the pooled results, based on the random-effects model, was conducted. The model was chosen over the fixed-effects model, as it is more suitable, and increases the generalizability of the findings (Guidi et al., 2011). For the hypothesized tests an alpha level of 0.05 was used.

To assess outliers and influential studies in the given model, studentized residuals and Cook's distances were inspected. "Studentized residuals greater than the 100 x (1 - 0.05/ (2 X k))th percentile of a standard normal distribution were considered potential outliers (i.e., using a Bonferroni correction with two-sided alpha = 0.05 for *k* studies included in the meta-analysis). Studies with a Cook's distance greater than the median and six times the interquartile range of the Cook's distances were regarded as influential" (Freitag et al., 2020, p. 5; Cook & Weisberg, 1982; Viechtbauer, 2010; Viechtbauer & Cheung, 2010). In case of outliers, sensitivity analysis was performed when deemed appropriate. In addition, the risk of publication bias and asymmetry were examined through Begg's funnel plot (Begg, 1994) and Egger's test statistic (Egger et al., 1997), respectively.

Results

Study selection

In the primary search 3,668 articles were identified. After removal of duplicates and screening of title and abstract, 45 relevant articles remained, of which 15 articles were excluded after full-text assessment. A total of 30 articles were ultimately included (total sample size *N*= 5,133,032, sample size per study presented a range from 30-4,794,466). The flow chart (see Figure 1) is illustrative of the search and selection process. From the final articles, 14 assessed the change of psychotropic prescription drug use and prescription dispensing in a comparative

manner (i.e., pre COVID-19 versus post COVID-19). Furthermore, 16 articles examined the impact of COVID-19 on changes of psychotropic prescription drug use. From the latter a total of 23 prevalence estimates for different types of drugs i.e., antipsychotics, SSRIs, SNRIs, CNS depressants, z-drugs, prescription opioids, and other psychotropic drugs, were extracted. Likewise, a total of 19 correlation coefficients were obtained from the 14 articles (see Figure 1).

The characteristics of the study are depicted in Table 1. The sample's mean age was 41.10 years (*SD* = 11.3), and females compromised 56.1% of participants. Furthermore, of the included studies 16 were cross-sectional, six were retrospective, five were time-series, one was observational, and two were descriptive studies, mostly conducted in North America (46.88%) and Europe (34.38%). In most studies, change in use of psychotropic prescription drugs related to COVID-19 was assessed through the use of self-report measures (43.75%). Other assessment methods were hospital/pharmacy data (21.87%), observational data (21.87%), laboratory data (9.38%), and 3.13% applied mixed measures.

Quality assessment

The included articles were evaluated with respect to methodological quality and risk of bias, which is depicted in Appendix A (see Table A1). The methodological quality scores presented a range from 4 to 9, with *M* = 7.13, and *SD* = 1.33. Overall, methodological quality scores were found to be good, with the exception of three articles being fair. Furthermore, the studies were generally clear in regards to the research question, study population, time-frame, measures, and assessment. The majority, however, did not thoroughly assess potential confounding variable's.

Figure 1. *Flowchart on identification, screening and inclusion of eligible publications*

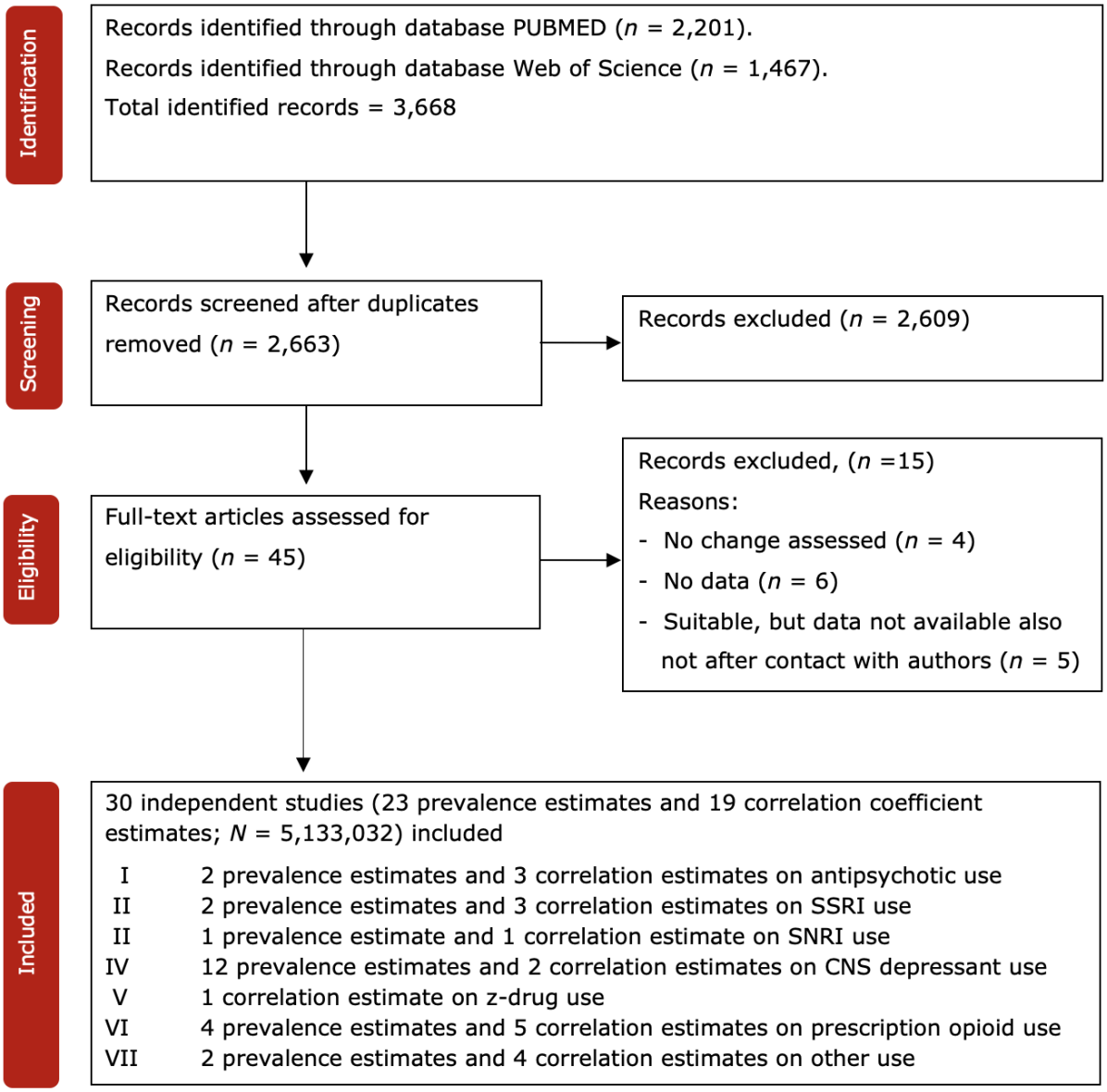


Table 1.

Characteristics of included studies and samples.

Study	Type of drug	*n*	Age [a]	Female %	Country
Aguilar et al. 2021	Stimulants and antidepressants	76	36.9	68	Brazil
Almandoz et al. 2021	Sedatives/tranquilizers, prescription opioids, stimulants	589	53.6	83	U.S.
Beck et al. 2021	Sleeping pills	1005	35	52	France
Brown et al. 2020	Antidepressants, anti-anxiety medication, naltrexone	1141	73	77	U.S.
Cance & Doyle 2020	Buprenorphine	66238	*N.K.*	*N.K.*	U.S.
Capuzzi et al. 2020	Psychotropic medication	613	44	50	Italy
Croxford et al. 2021	Pregabalin	3546	41	25	U.K.
Di Lorenzo et al. 2021	Therapeutic drug prescriptions	1467	43	54	Italy
Diez-Quevedo et al. 2021	Antidepressants, antipsychotics, benzodiazepines	2150	61.3	43	Spain
Fayed and Sharif 2021	Antipsychotics	1916	*N.K.*	*N.K.*	Egypt
Gili et al. 2021	Benzodiazepines	30	30	43	Italy
Gras et al. 2021	Antidepressants, antipsychotics, opioids	319	30.5	57	France
Grigsby et al. 2021 (a)	Anti-anxiety medication	680	21	39	U.S.
Grigsby et al. 2021 (b)	Sleep aids	757	21	44	U.S.
Gritsenko et al. 2020	Psychostimulants, pain relievers, and sedatives	939	21.8	81	Russia & Belarus
Hochstatter et al. 2021	Prescription opioids	342	41.1	52	U.S.
Joyce et al. 2020	Opioids, muscle relaxants, and neuropathic pain medications	260	48.6	14	U.S.
Khatri et al. 2021	Naloxone	1507	*N.K.*	*N.K.*	U.S.
Khurana et al. 2020	Prescription morphine, tramadol, fentanyl	5471	*N.K.*	*N.K.*	India
Lacasse et al. 2021	Prescription opioids	2864	49.7	84	Canada
Leira-Sanmartín et al. 2021	Psychotropic drugs	647	41.1	79	Spain
Macía-Rodríguez et al. 2021	Sleeping pills	1015	39.9	63	Spain
Mandelkorn et al. 2021 (a)	Sleeping pills	2562	45.2	68	Mix [b]
Mandelkorn et al. 2021 (b)	Sleeping pills	971	40.4	53	U.S.
McGraw et al. 2021	Opiates, benzodiazepines, barbiturates	1025	41.1	28	U.S.
Papp & Kouros 2021	Prescription drug misuse	295	19.5	71	U.S.
Salas-Nicas et al. 2021	Tranquilizers/sedatives, prescription opioids	20328	41.1	58	Spain
Sánchez Díaz et al. 2021	Benzodiazepines	4794466	*N.K.*	*N.K.*	Spain
Stall et al. 2021	Antipsychotics, antidepressants, benzodiazepines, trazadone	77291	*N.K.*	*N.K.*	Canada
Thornton et al. 2020	Buprenorphine	138615	*N.K.*	*N.K.*	U.S.
Vicario et al. 2020	Psychotropic drugs	3542	60.2	55	Argentina
Yu et al. 2020	Antidepressants, benzodiazepines, z-drugs	365	46.8	61	Canada

Note.

[a] Average age.

[b] Argentina, Armenia, Brazil, Canada, Chile, Colombia, France, Germany, Israel, Italy, Kazakhstan, Peru, Portugal, Romania, Russian Federation, Spain, United Kingdom, USA, Other

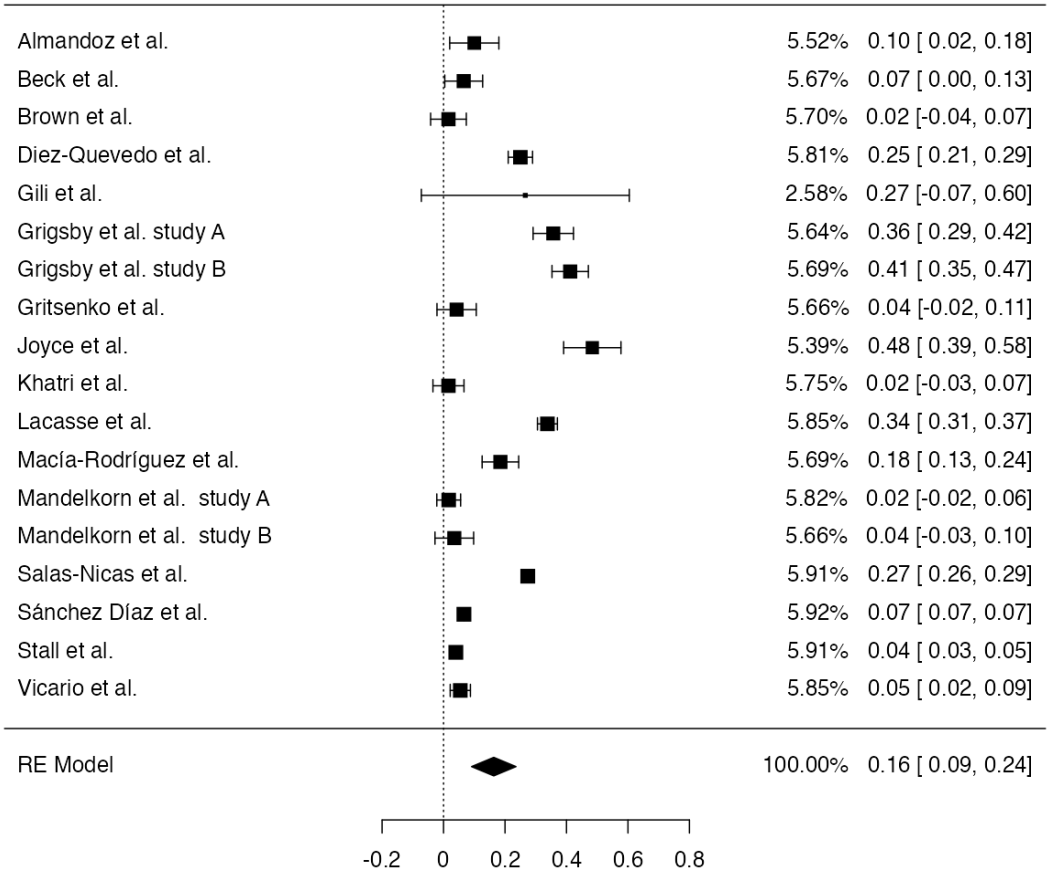
Meta-analysis

Main Effects

In the first analysis of the current meta-analysis, a total of 16 studies (k = 18) were entered. The prevalence estimates of psychotropic prescription drug use presented a range from 1.6% to 48.4%. The pooled estimated prevalence based on the random-effects model was 16.34% (95% CI: 9.11 to 23.57; z = 4.4316, p < 0.0001). Between-study heterogeneity in outcome was found to be high and significant (Q(17) = 1741.3918 , I^2 = 99.7%, p < .0001; see Figure 2). No publication bias was observed

Figure 2.

Forest plot of estimated prevalence change of psychotropic prescription drug use



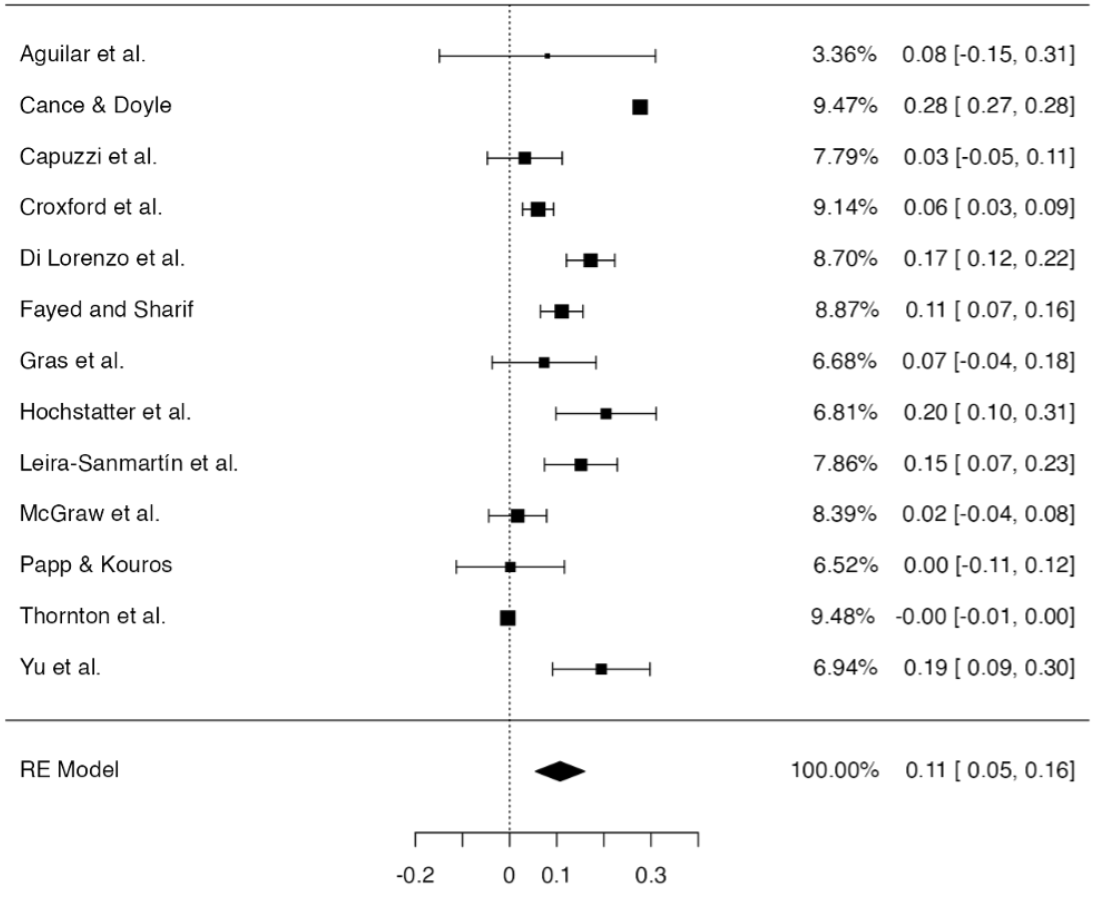
Note. The studies are ordered by fitted values (with 95% confidence intervals).

In the second analysis of the current meta-analysis, a total of 14 studies (k = 14) were included. The correlation coefficients ranged from -0.24807 to 0.2735. The pooled estimated correlation coefficient based on the random-effects model was r = 0.0781 (95% CI: 0.0080 to

0.1483; $z = 2.1821$, $p = 0.0291$). Heterogeneity was found to be high and significant ($Q(13) = 4046.1807$, $I^2 = 99.2958\%$, $p < .0001$). An inspection of the studentized residuals and Cook's distance revealed that one study (Khurana et al., 2020) had a value larger than ± 2.9137 and therefore was considered a possible outlier and exceedingly influential in the framework of this model. Therefore, a sensitivity analysis excluding the study was performed to assess how this change may impact the conclusion of our primary analysis. After removal of the outlier, the correlation coefficients ranged from -0.0040 to 0.2769. The pooled estimated correlation coefficient based on the random-effects model was $r = 0.1070$ (95% CI: 0.0546 to 0.1593; $z = 4.0041$, $p < 0.0001$). Heterogeneity remained high and significant ($Q(12) = 3570.1256$, $p < 0.0001$, $tau^2 = 0.0075$, $I^2 = 98.5150\%$). The Forest Plot, depicted in Figure 3, illustrates the entered studies, ordered by fitted values (with 95% confidence intervals).

Figure 3.

Forest plot of correlation estimates of prescription psychotropic drug use and dispensing



Note. The studies are ordered by fitted values (with 95% confidence intervals).

Subgroup effects

Table 2 provides pooled prevalence estimates based on the random-effects model for type of drug use (i.e., CNS depressants and prescription opioids). The prevalence estimates of CNS depressant use and prescription opioid use were both statistically significant. Prevalence estimates of prescription opioid use was slightly higher with a difference of 4%. Forest plots on these estimates can be found in Appendix B (see Figure B1 and B2). High and significant heterogeneity was evident in both analyses.

Table 2.

Prevalence of CNS depressant and prescription opioid use.

Drug class	*k*	*n*	Prevalence (95% CI)	*Z*	I^2	*Q*
CNS Depressants	11	4901179	0.14 (0.05 – 0.23)	3.1007**	99.78	833.5469***
Prescription Opioids	4	24391	0.18 (0.04 – 0.31)	2.5591*	98.02	164.0909***

Note. Random-effects model.

*$P < 0.05$; **$P < 0.01$; ***$P \leq 0.001$

Table 3 provides results of further analyses using the random effects model on type of drug use (i.e., antipsychotics, antidepressants, and prescription opioids). The corresponding forest plots for each drug type can be found in Appendix B (see Figure B3 - B5). Based on the random-effects model, the pooled effect for antipsychotic use differed significantly from zero. Whereas antidepressant use and prescription opioid use did not differ significantly from zero. According to the *Q*-test, no significant amount of heterogeneity was found for correlation coefficient estimates of antipsychotic drug use. Whereas the correlation coefficient estimates of antidepressant and prescription opioid use appeared heterogenous. In addition, no publication bias was observed in all the analyses (see Figure C1-C3).

Table 3.

Correlation coefficient estimates of antipsychotic, antidepressant, and prescription opioid use.

Drug class	*k*	*n*	*r* (95% CI)	*z*	I^2	*Q*
Antipsychotics	3	3260	0.08 (0.03 – 0.13)	3.0546**	47.31	3.6792
Antidepressants	3	760	0.16 (-0.06 – 0.37)	1.4425	86.33	18.0281***
Prescription Opioids	5	211668	0.02 (-0.14 – 0.19)	0.2623	99.88	4014.9389***

Note. Random-effects model.

*$P < 0.05$; **$P < 0.01$; ***$P \leq 0.001$

Moderator effects

To address and account for the high between-study variability, seven moderator variables (i.e., average age, gender distribution, continent, study design, measures used, medical and non-medical use, and population) were tested. Prevalence rates of psychotropic prescription drug use were found to be significantly associated with gender distribution, with an estimated prevalence of - 47% (95% CI: -85 to -9, $p = 0.0149$). Thus, suggesting that lower prevalence rates of prescription psychotropic drug use might be observed in studies with a higher proportion of female participants (see Figure B6). This is depicted in Figure B7, in which studies are presented by proportion of female participants in descending order. Publication bias was not observed as assessed through Begg's funnel plot (Begg, 1994; see Figure C4-C5), which indicated no asymmetry, and Egger's test statistic (Coefficient = 0.9000 , $p = 0.3681$; Egger et al., 1997).

The prevalence rates of CNS depressants use were found to be significantly associated with gender distribution with an estimated prevalence of -0.907 (95% CI: -1.47 to -0.45, $p = 0.0015$). Thus, suggesting that lower prevalence rates of CNS depressant use might be observed in studies with a higher proportion of female participants (see Figure B8). This is depicted in Figure B9, in which studies are presented by proportion of female participants in descending order. No publication bias was observed (Coefficient = 0.8896, $p = 0.3737$; Egger et al., 1997; see Figure C6-C7).

Furthermore, the moderator 'continent' was found to be significantly associated with prevalence rates of prescription opioid use, with an estimated prevalence of -11.40 % (95% CI: -21 to -7, $p < 0.0001$; see figure A10). Thus, suggesting that higher prevalence rates of prescription opioid use might be observed in studies conducted in North America (see Figure B11). In addition, publication bias was not observed (Coefficient = 0.0066, $p = 0.9947$; Egger et al., 1997; see C8-C9).

Estimated correlation coefficients of psychotropic prescription drug use did not differ as a function of average age, gender distribution, continent, study design, measures used, medical and non-medical use, or population. Additionally, no publication bias was observed, which has been assessed through Begg's funnel plot (Begg, 1994; see Figure C10), indicating no funnel plot asymmetry, and Egger's test statistic (Coefficient = -0.2627, $p = 0.7928$; Egger et al., 1997).

Discussion

The present one-year systematic review and meta-analysis of cross-sectional, retrospective, observational, descriptive, and time-series studies, examined any change in use, dispensing, and filling of prescription psychotropic drugs related to COVID-19 (i.e., any change of pre COVID-19 relative to post COVID-19). Furthermore, the study conducted exploratory analyses to assess changes in specific types of prescription psychotropic drug use, as well as potential sources of heterogeneity. It was hypothesized that COVID-19 is related to increased psychotropic prescription drug use and prescribing practices. Two separate analyses were conducted. The results and their implications will be discussed below.

Main Findings

In line with the hypothesis of COVID-19 being related to increased psychotropic prescription drug use, the findings demonstrate a statistically significant increase of 16.34% in prevalence estimates of psychotropic prescription drug use that may be attributed to the COVID-19 pandemic. Similarly, a small positive statistically significant correlation (Cohen, 1988) was yielded, implying a small increase of psychotropic prescription drug use relative to pre and post COVID-19. The findings accord with earlier observations, provided by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA; 2020), which found an increase in frequency and amount of prescription drug use among individuals struggling with their mental health (i.e., depression, anxiety), during the COVID-19 pandemic. This may be explained by individuals' maladaptive coping mechanisms in response to the confinement measures (EMCDDA; 2020).

As mentioned in the literature review, changes in psychotropic prescription drug use reported among several studies are not in parallel, suggesting probable heterogeneity between studies. In fact, high and significant heterogeneity was evident in the conducted meta-analysis. To obtain a better understanding of between-study heterogeneity, moderator analyses were conducted aimed to identify the sources of variation. As such, prevalence estimates of psychotropic prescription drug use were found to differ as a function of gender distribution. When looking at the figure, the moderator analyses revealed that changes in psychotropic prescription drug use, which may be due to COVID-19, are less apparent in samples with a higher proportion of female participants. Numerous studies examining psychotropic prescription drug use and abuse have highlighted differences among gender. Surprisingly, most findings

report a higher prevalence of psychotropic drug use among women. While the consumption of overall psychotropic drug use is found to be higher in females, some studies report higher prevalence among men, or similar prevalence among both genders for opioid use (McHugh et al., 2015). Another factor which may contribute to the observed gender differences in psychotropic prescription drug use is the physician's view towards gender and the need for psychotropic medications (Moreno Luna et al., 2000). Qualitative research indicates that physicians evaluate perceived symptoms of common mental health disorders (e.g., anxiety, depression) differently depending on the patient's gender (Estancial Fernandes et al., 2018). The contradictory finding in the present meta-analysis might be due to inconsistent definitions of use/misuse of psychotropic prescription drugs across countries. Another possible explanation might be due to rising mental health problems in relation to COVID-19, such as anxiety, depression, and insomnia, with the latter being a strong predictor for psychotropic drug abuse among men (Estancial Fernandes et al., 2018). Furthermore, one unanticipated finding was that differences in prevalence estimates of psychotropic prescription drug use did not differ as a function of age. This finding was surprising, since age is another common factor associated with psychotropic prescription drug use, with studies generally showing an increase among older populations, especially the elderly (Blay et al., 2014; Quintana et al., 2015).

Exploratory Findings

The exploratory analyses on type of psychotropic drug use indicate an increase of 14% and 18% in prevalence estimates of CNS depressant and opioid use, respectively. This finding is in line with prior research, revealing an overall increase in anxiolytic, sedative, and hypnotic use in Europe Estrela et al. (2020). Likewise, a meta-analysis conducted prior to COVID-19 reported an increase of 0.4% in prevalence estimates of prescription opioid misuse [Jordan et al., 2017, #258757]. While another study by Huerta et al. (2016), comparing trends in prescribing benzodiazepines from 2001 to 2009, found that standardized prevalence rates increased in Spain (13%) and the UK (2% to 8%), whereas a decrease was found in other European countries such as Germany (-12%), the Netherlands (-4% to -22%), and Denmark (-26%). Moreover, non-significant correlations for antidepressant, and prescription opioid use relative to pre and post COVID-19 were yielded, suggesting no change. Whereas a weak statistically significant correlation for antipsychotics was found.

Noteworthy, moderator analyses revealed that changes in CNS depressant use, which might be due to COVID-19, are less apparent in samples with a higher proportion of female participants. Numerous studies examining prescription drug use and abuse have highlighted differences among gender. Moreover, prevalence rates of prescription opioid use were found to differ as a function of 'continent'. Changes of prescription opioid use were more apparent in studies conducted in North America. This might imply that differences in use, dispensing, and prescription of opioids exist among the countries. This is in line with findings of the United Nations Office on Drugs and Crime [UNODC] (2021), who report the following annual prevalence of prescription opioids in 2018 for the US (4.3), Finland (0.9), Estonia (0.13), and the United Kingdom (0.06). These differences may be explained by the availability and prescribing practices of psychotropic prescription drugs in the individual countries.

Strength and Limitations of the Study

The findings from this study make several contributions to the current literature. Primarily, it is the first meta-analysis that assessed changes in psychotropic prescription drug use in relation to COVID-19. The findings of the study enhance our understanding about the potential impact COVID-19 may have on prescription drug use, misuse, and abuse.

Meta-analyses provide the ability to assess and integrate results of analogous studies. As a result, statistical power and number of observations are strengthened, and the correlation and prevalence estimates of effect size are ameliorated (Fagard et al., 1996). Therefore, the study design is an advantage itself. Furthermore, the study's inclusion criteria regarding language and the target population (i.e., clinical, and general population) safeguards external validity, as the study's results are generalizable (Cooper et al., 2019; Littell et al., 2008). In addition, the study makes use of pharmacy and hospital databases, medical records, registers, and independently collected data, which minimizes selection bias (Thygesen & Ersbøll, 2014). Also, several rounds of data extraction safeguarded construct validity, to the best of the author's knowledge, it was assured that the included articles measured what they intended to measure (Kazdin, 2017). Moreover, the study screened for publication bias, which could have increased risk of bias (Begg, 1994; Rothstein et al., 2005). Lastly, the study took corrective measures of overly influential outliers with post-hoc conducted sensitivity analyses, to assess the strength and consistency of the results under different assumptions and decisions made during the review

process. The removal of the overly influential outlier resulted in a more robust and statistically significant correlation. Therefore, strengthening the credibility of the findings (Thabane et al., 2013).

Next to the strengths, some limitations need to be acknowledged. Firstly, the validity of the results of the meta-analysis are contingent on the quality of the information provided in the included individual studies (Greco et al., 2013). Secondly, while many languages were included, the fact of the matter is almost all studies were reported in the English language and reported in western countries. Therefore, external validity is affected, because the included studies might not be representative of all potentially relevant studies (Littell et al., 2008). Furthermore, some sample characteristics (i.e., age and gender) were missing and therefore, the average age, and proportion of females of the sample population was imputed.

It should be noted, that due to the limitations of meta-analyses, the findings do not confer causality of COVID-19 on psychotropic prescription drug use, but rather their potential association (Greco et al., 2013). Furthermore, some studies reported the prevalence/ correlation of more than one type of drug. Therefore, the average effect size was imputed in the pooled prevalence/correlation estimate for the given study. Lastly, subgroup analyses could not be conducted, because types of drugs were not reported evenly in the included studies. Similarly, it was not possible to conduct a subgroup analysis on at-risk populations (i.e., pre-existing mental illness vs those without), due to lack of data. Although moderator analyses were conducted when heterogeneity was evident, much of the between-study variation remained unaccounted for. Between-study heterogeneity may be due to inconsistency in definitions of prescription drug use, misuse, and abuse across studies.

Research implications and recommendations

CNS depressants (i.e., benzodiazepines, z-drugs, sedatives, etc.) are among the most frequently prescribed psychotropic drugs in the world (Agarwal & Landon, 2019; Grohol, 2019). The sedative, sleep-inducing effects of these drugs, make them beneficial for the treatment of anxiety and panic disorders (Schmitz, 2016). However, CNS depressants have a significant potential for abuse and misuse, and are often associated with prolonged withdrawal syndrome, especially if stopped abruptly (Schmitz, 2016). Given the rising concern regarding the risks and safety of psychotropic prescription drugs, overdose related deaths, addictions, and prolonged

withdrawal syndromes (Agrawal, 2020), as well as the mental health crisis expected to be caused by the COVID-19 pandemic, it is necessary to understand the use and prescribing practices of different psychotropic drugs during the COVID-19 pandemic relative to pre-pandemic times. This meta-analysis yielded noteworthy findings, implying a small increase of psychotropic prescription drug use within one year. Since the COVID-19 pandemic has still not reached an end, it may be beneficial to assess and compare the psychotropic drug use relative to pre-and post-pandemic with a third time point. This would highlight the true effect that COVID-19 may have on psychotropic prescription drug use. Furthermore, given that the countries imply different measurements, which have been loosened and restricted over time, it would be beneficial to compare the psychotropic drug use by country at a later stage as the pandemic evolves.

Future Research

Moreover, future research should address populations at risk (e.g., people with pre-existing mental illness, frontline workers) since it can help mitigate exacerbation of mental illness, reduce suicidal ideation, and aid in alleviating long-term morbidity and mortality caused by the pandemic (Gobbi et al., 2020). Future research on this topic is recommended, as it is a timely matter with detrimental consequences, which will only become more apparent as the pandemic progresses.

Conclusion

To conclude, the present one-year systematic review and meta-analysis examined the change in use, dispensing, and filling of prescription psychotropic drugs related to COVID-19 (i.e., any change of pre COVID-19 relative to post COVID-19). Furthermore, the study conducted exploratory analyses to assess changes in specific types of prescription psychotropic drug use, as well as potential sources of heterogeneity. The association between COVID-19 and adverse mental health, as well as the increased use of psychotropic medications, may lead to an upsurge in substance use related disorders and overdose-related deaths. Given the interruptions to many substance use treatment programs during the pandemic. It may be important for policy makers and health officials to address mental and behavioral health through telemedicine.

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Appendix A: Quality Assessment

Table A1
Quality assessment by study.

Study	1	2	3	4	5	6	7	8	9	11	14	Total
Aguilar et al. 2021	⊕	⊕	⊕	⊕	⊕	∅	⊕	∅	⊕	⊕	∅	8
Almandoz et al. 2021	⊕	⊕	⊕	⊕	⊕	∅	⊕	∅	⊕	⊕	⊕	9
Beck et al. 2021	⊕	⊕	⊕	⊕	⊕	∅	⊕	∅	⊕	⊕	∅	8
Brown et al. 2020	⊕	⊕	⊕	⊕	∅	∅	⊕	∅	∅	⊕	∅	6
Cance & Doyle 2020	⊕	∅	⊕	⊕	⊕	∅	⊕	∅	⊕	⊕	⊗	6
Capuzzi et al. 2020	⊕	⊕	⊕	⊕	⊕	∅	⊕	∅	⊕	⊕	⊕	9
Croxford et al. 2021	⊕	⊕	⊕	⊕	⊕	∅	⊕	∅	⊕	⊕	⊗	7
Di Lorenzo et al. 2021	⊕	⊕	⊕	⊕	⊕	∅	⊕	∅	⊕	⊕	∅	8
Diez-Quevedo et al. 2021	⊕	⊕	⊕	⊕	⊕	∅	⊕	∅	⊕	⊕	∅	8
Fayed and Sharif 2021	⊕	∅	⊕	⊕	∅	∅	⊕	∅	⊕	⊕	⊗	5
Gili et al. 2021	⊕	⊕	⊕	⊕	⊕	∅	⊕	∅	⊕	⊕	∅	8
Gras et al. 2021	⊕	∅	⊕	⊕	⊕	∅	⊕	∅	⊕	⊕	⊗	6
Grigsby et al. 2021 (a)	⊕	⊕	⊕	⊕	⊕	∅	⊕	∅	⊕	⊕	⊗	7
Gritsenko et al. 2020	⊕	⊕	⊕	⊕	∅	∅	⊕	∅	⊕	⊕	⊗	6
Hochstatter et al. 2021	⊕	⊕	⊕	⊕	⊕	∅	⊕	∅	⊕	⊕	∅	8
Joyce et al. 2020	⊕	⊕	⊕	⊕	⊕	∅	⊕	∅	⊕	⊕	∅	8
Khatri et al. 2021	⊕	⊕	⊕	⊕	∅	∅	⊕	∅	∅	∅	⊗	4
Khurana et al. 2020	⊕	⊕	⊕	⊕	⊕	∅	⊕	∅	⊕	⊕	⊗	7
Lacasse et al. 2021	⊕	⊕	⊕	⊕	⊕	∅	⊕	∅	⊕	⊕	∅	8
Leira-Sanmartín et al. 2021	⊕	⊕	⊕	⊕	⊕	∅	⊕	∅	⊕	⊕	⊕	9
Macía-Rodríguez et al. 2021	⊕	⊕	⊕	⊕	⊕	∅	⊕	∅	⊕	⊕	∅	8
Mandelkorn et al. 2021 (a)	⊕	⊕	⊕	⊕	⊕	∅	⊕	∅	⊕	⊕	∅	8
McGraw et al. 2021	⊕	⊕	⊕	⊕	⊕	∅	⊕	∅	⊕	⊕	⊗	7
Papp & Kouros 2021	⊕	⊕	⊕	⊕	⊕	∅	⊕	∅	⊕	⊕	⊕	9
Salas-Nicas et al. 2021	⊕	∅	⊕	⊕	∅	∅	⊕	∅	⊕	⊕	∅	6
Sánchez Díaz et al. 2021	⊕	∅	⊕	⊕	∅	∅	⊕	∅	⊕	⊕	⊗	5
Stall et al. 2021	⊕	⊕	⊕	⊕	∅	∅	⊕	∅	⊕	⊕	⊗	6
Thornton et al. 2020	⊕	⊕	⊕	⊕	∅	∅	⊕	∅	⊕	⊕	⊗	6
Vicario et al. 2020	⊕	⊕	⊕	⊕	∅	∅	⊕	∅	⊕	⊕	⊗	6
Yu et al. 2020	⊕	⊕	⊕	⊕	∅	∅	⊕	∅	⊕	⊕	⊕	8

Note. For the methodological quality assessment of the included studies, the Quality Assessment Tool for Observational Cohort and Cross-Sectional studies was used (United States National Institutes of Health; https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools) . Of the 14 criteria items, three were deemed unsuitable.

⊕ = Yes

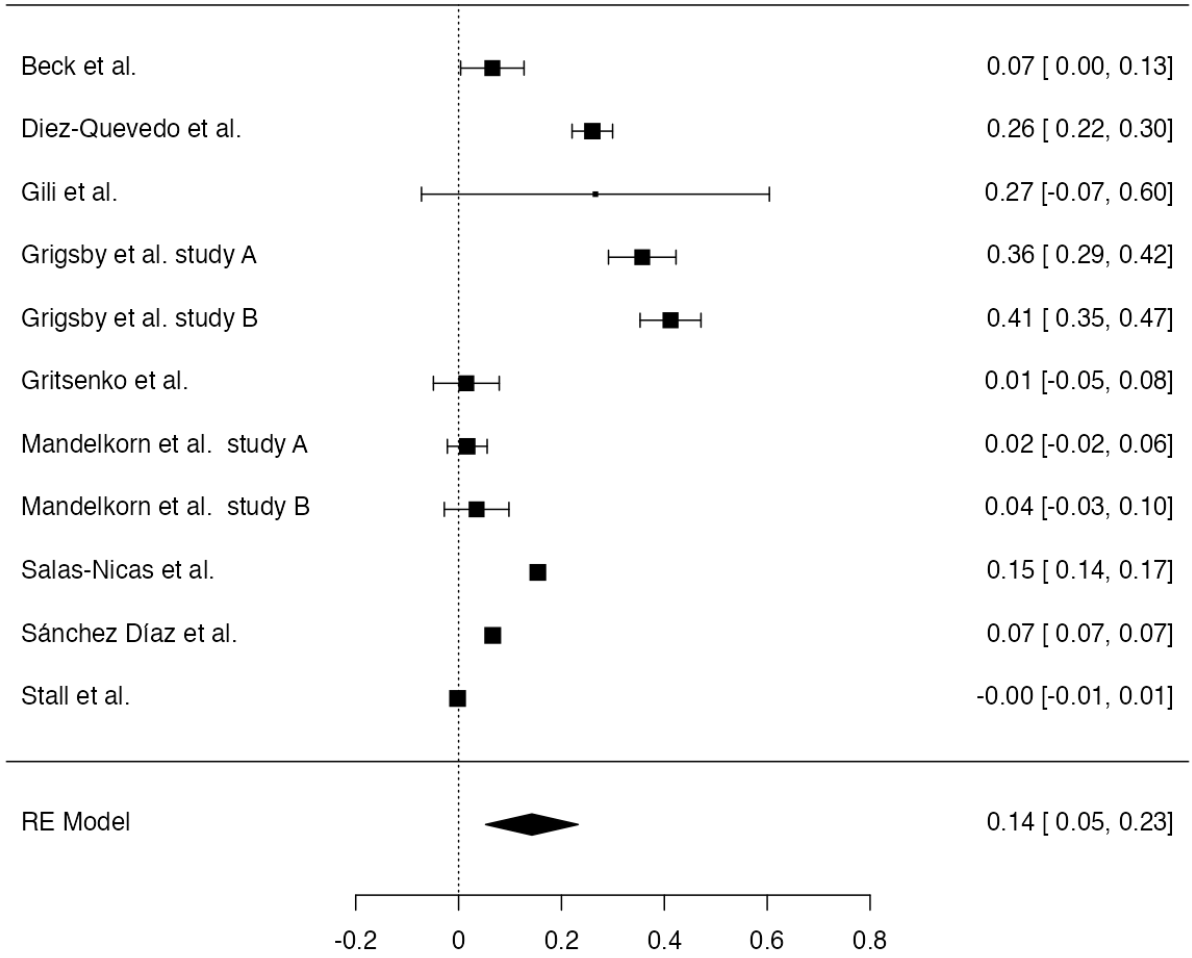
⊗ = No

∅ = Neutral/ not sure/ not applicable

Appendix B: Forest Plots

Figure B1.

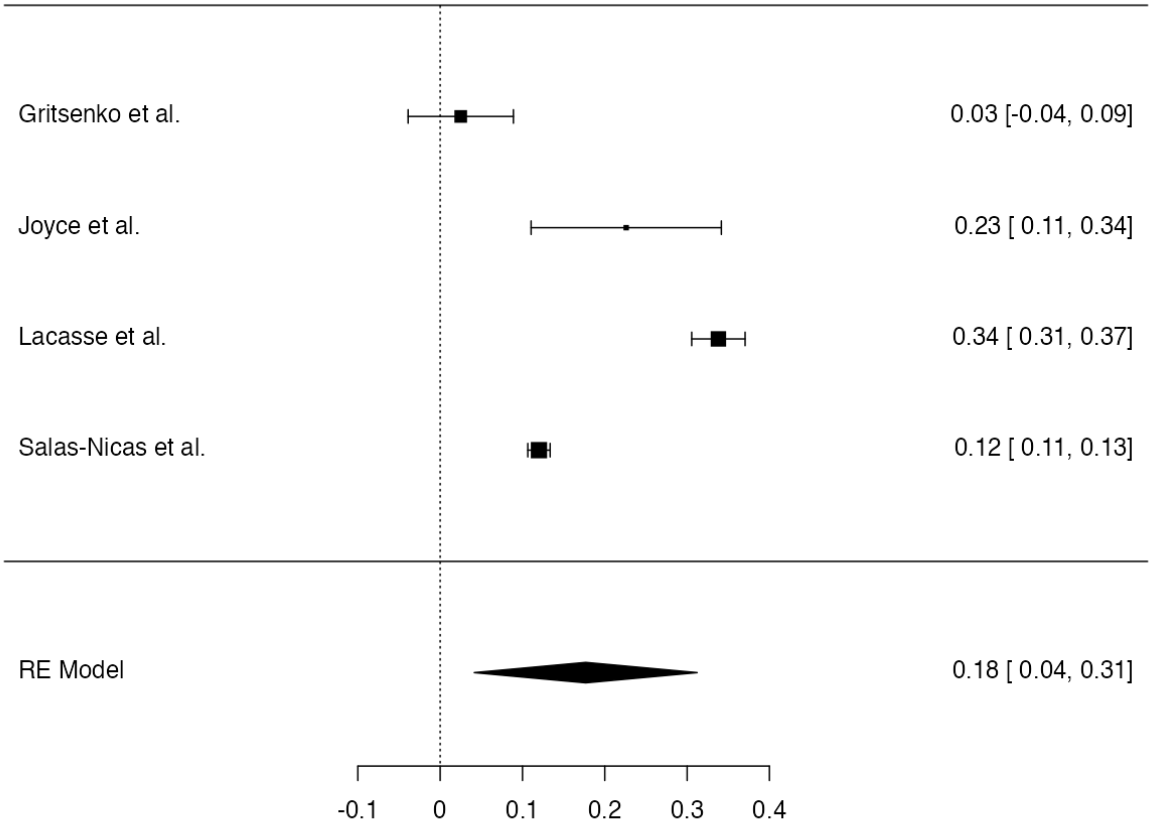
Forest plot of prevalence estimates of *CNS depressant drug use.*



Note. The studies are ordered by fitted values (with 95% confidence intervals).

Figure B2.

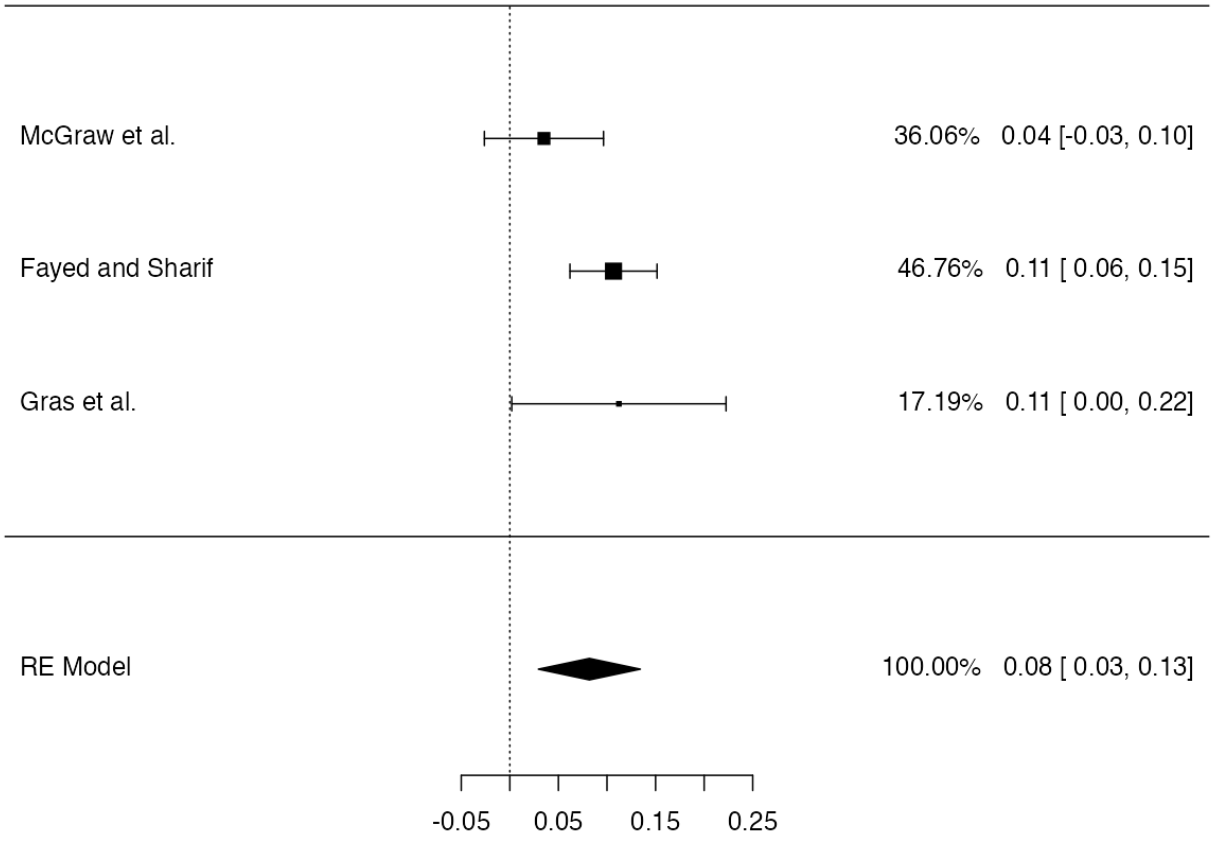
Forest plot of prevalence estimates of prescription opioid use.



Note. The studies are ordered by fitted values (with 95% confidence intervals).

Figure B3.

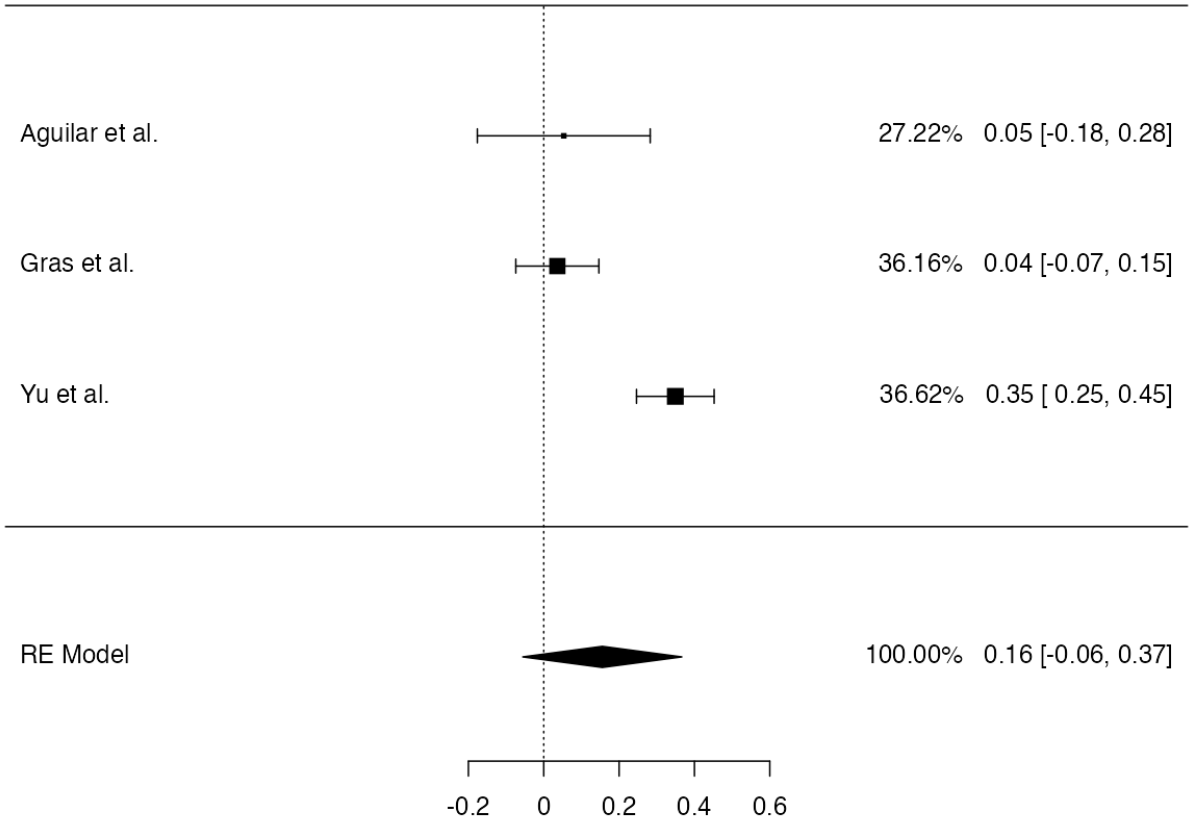
Forest plot of correlation coefficient estimates of antipsychotic use.



Note. The studies are ordered by fitted values (with 95% confidence intervals).

Figure B4.

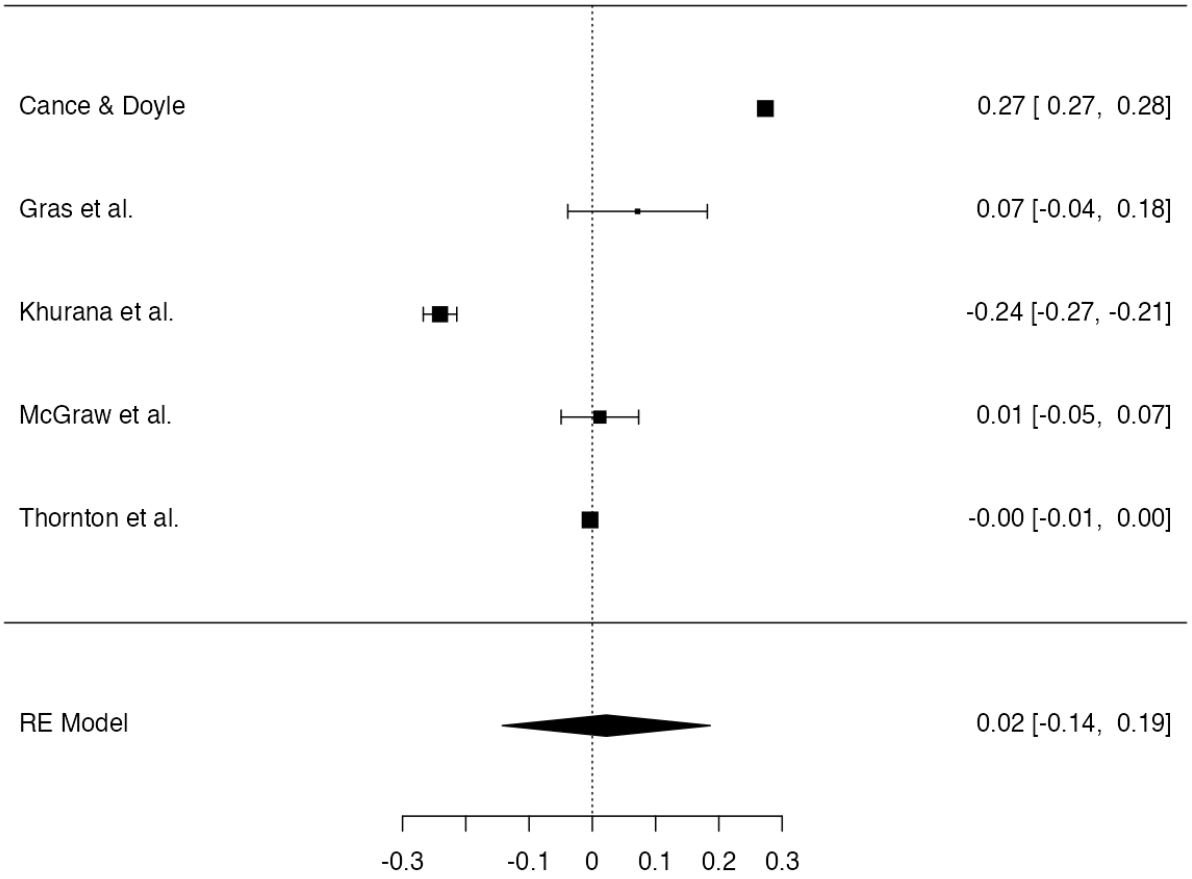
Forest plot of correlation coefficient estimates of antidepressant use.



Note. The studies are ordered by fitted values (with 95% confidence intervals).

Figure B5.

Forest plot of correlation coefficient estimates of prescription opioid use



Note. The studies are ordered by fitted values (with 95% confidence intervals).

Figure B6.

Regression of the moderator gender distribution on prevalence estimates of prescription psychotropic drug use.

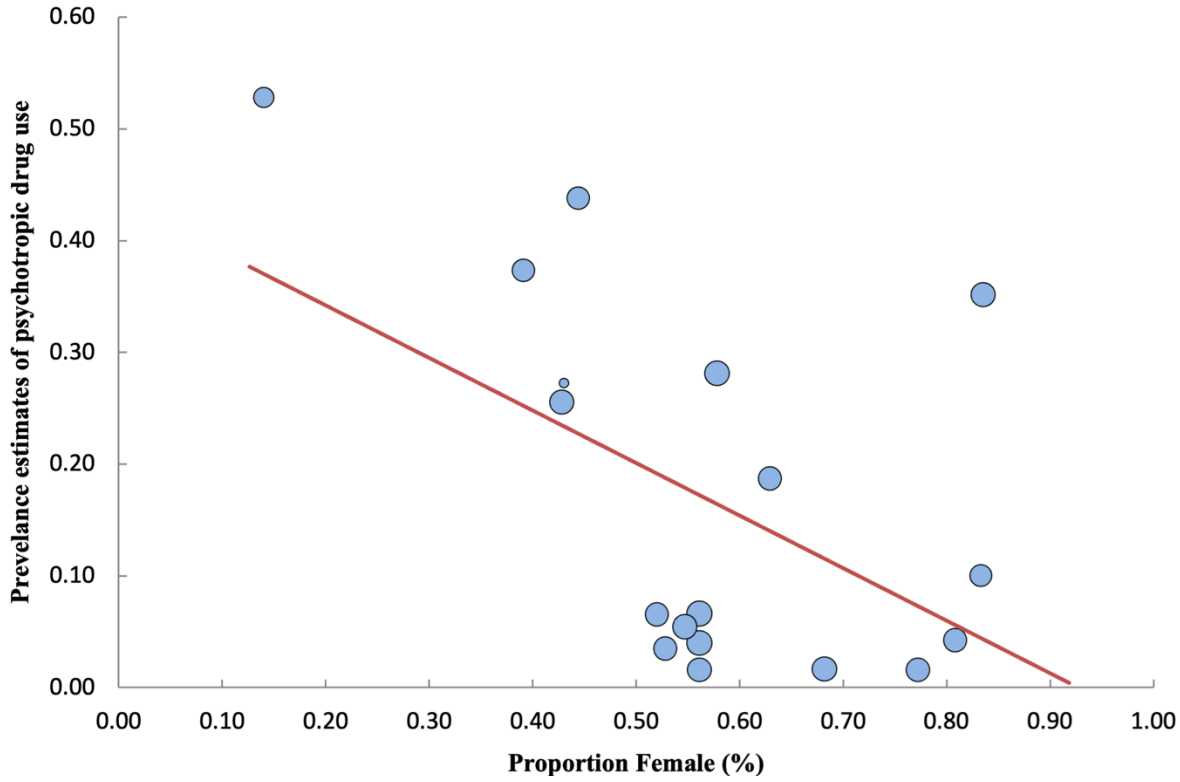
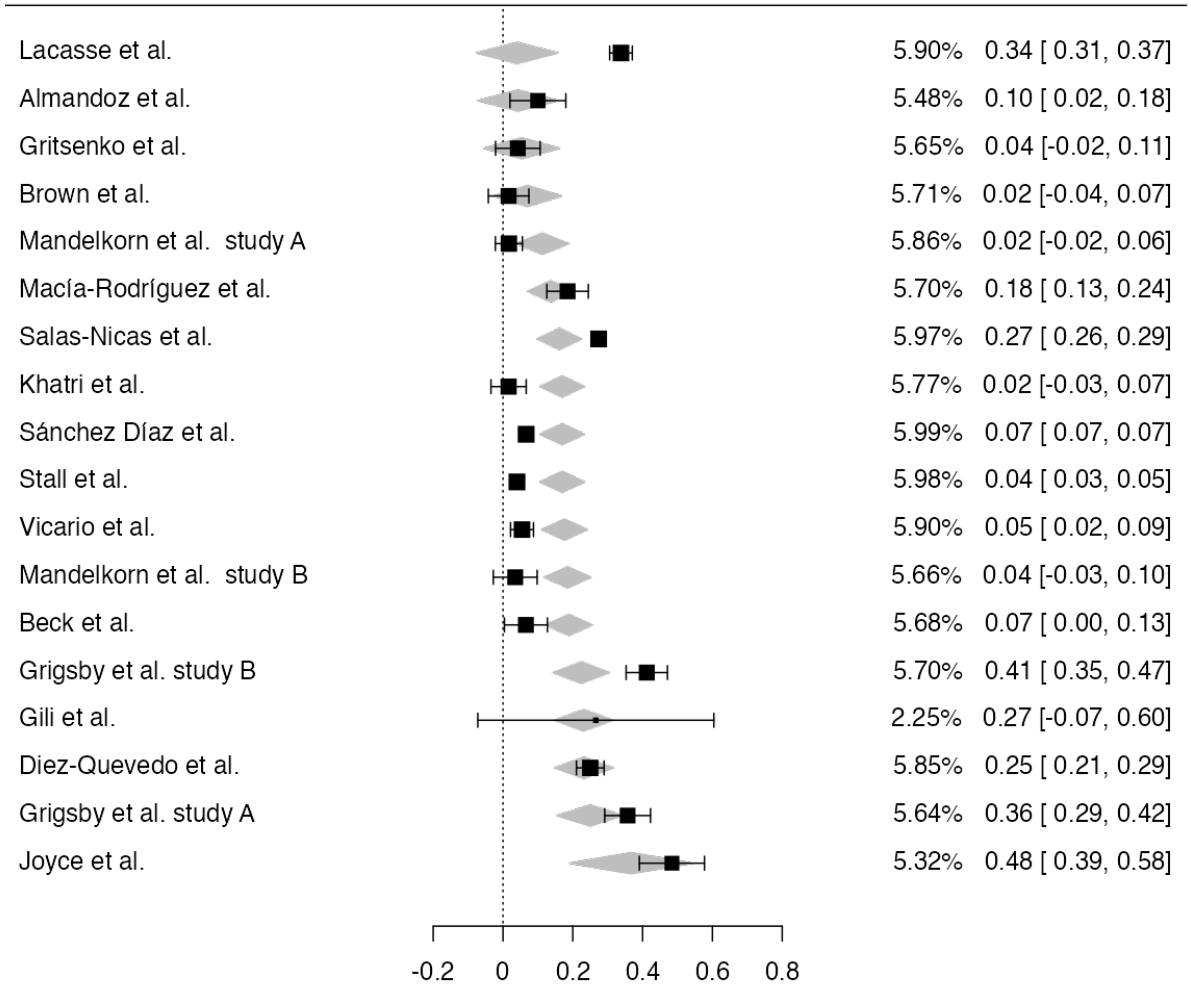


Figure B7.

Forest plot of estimated prevalence of psychotropic prescription drug use by gender distribution.



Note. Studies are ordered from highest to lowest proportion of female participants (with 95% confidence intervals).

Figure B8.

Regression of the moderator gender distribution on prevalence estimates of central nervous system depressant drug use.

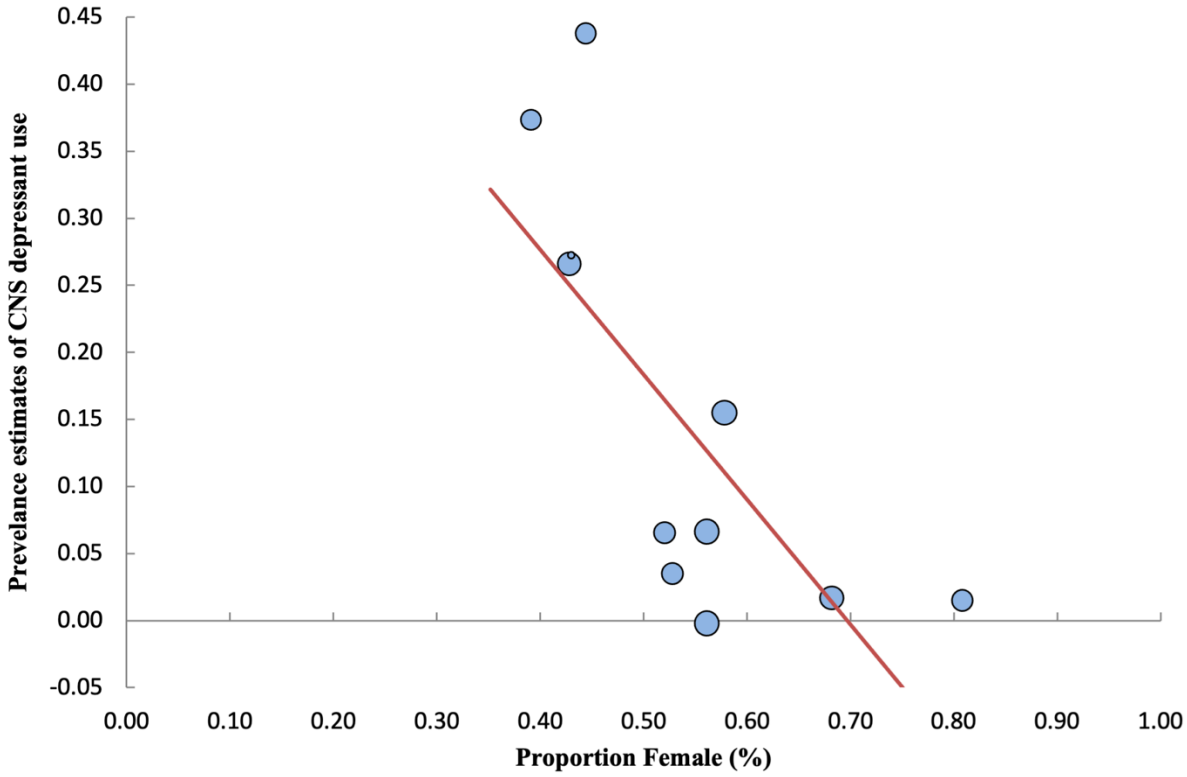
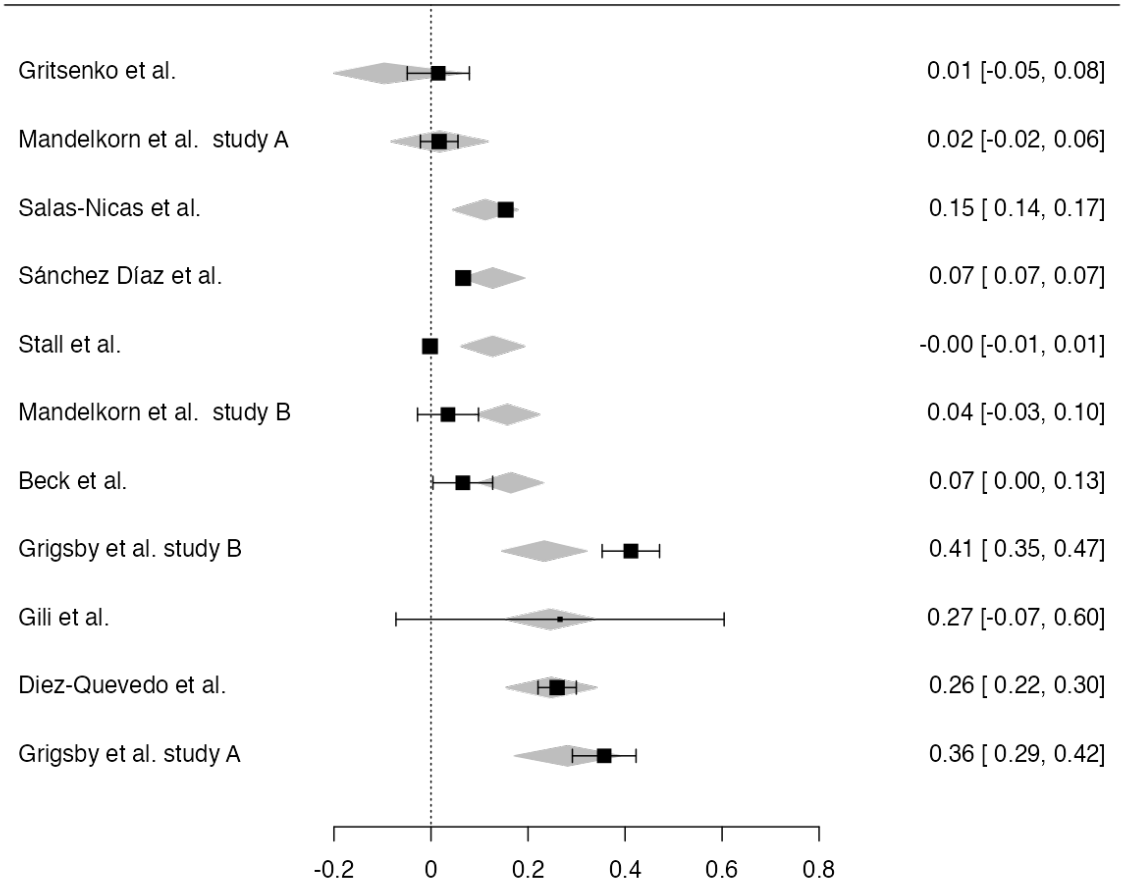


Figure B9.

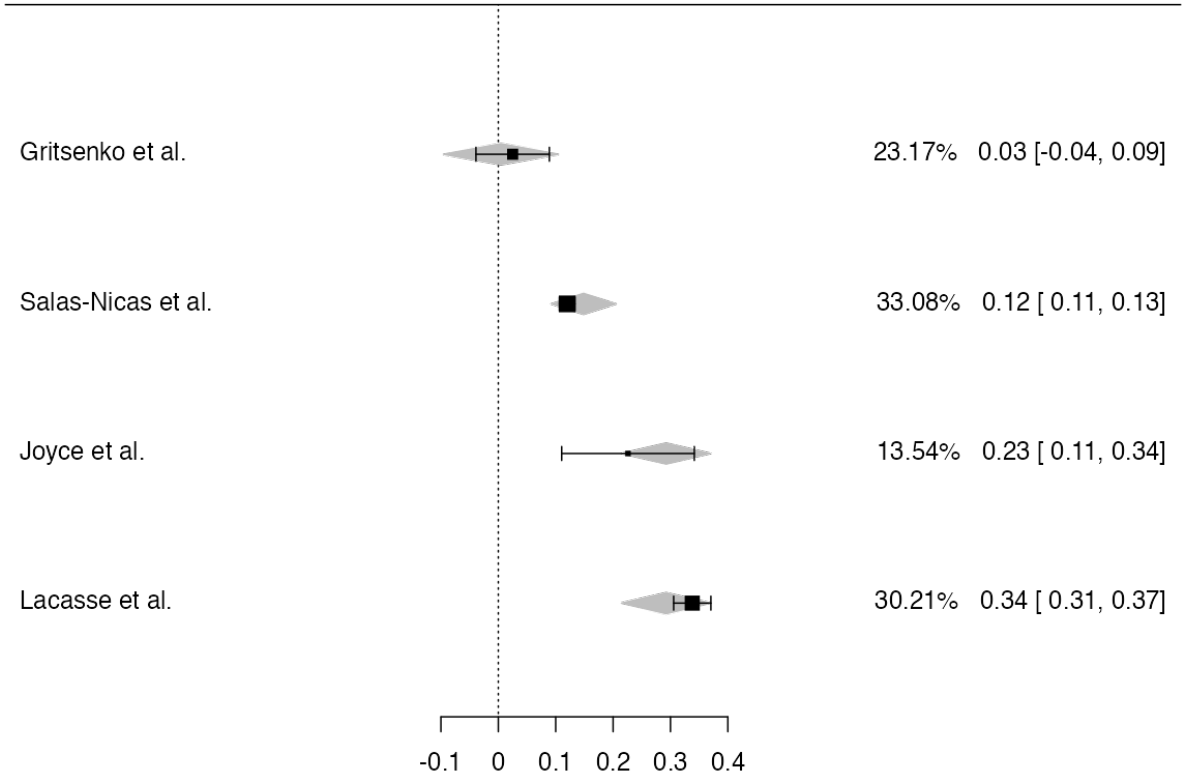
Forest plot of prevalence estimates of CNS depressant use as a function of gender distribution.



Note. Studies are ordered from highest to lowest proportion of female participants (with 95% confidence intervals).

Figure B10.

Forest plot of prevalence estimates of prescription opioid use by continent.



Note. The studies are ordered by fitted values (with 95% confidence intervals).

Mix (Russia and Belarus) - Gritsenko et al.

Europe - Salas-Nicas et al

North America – Joyce et al., Lacasse et al.

Appendix C: Funnel Plots

Figure C1.

Funnel plot of correlation coefficient estimates of antipsychotic use

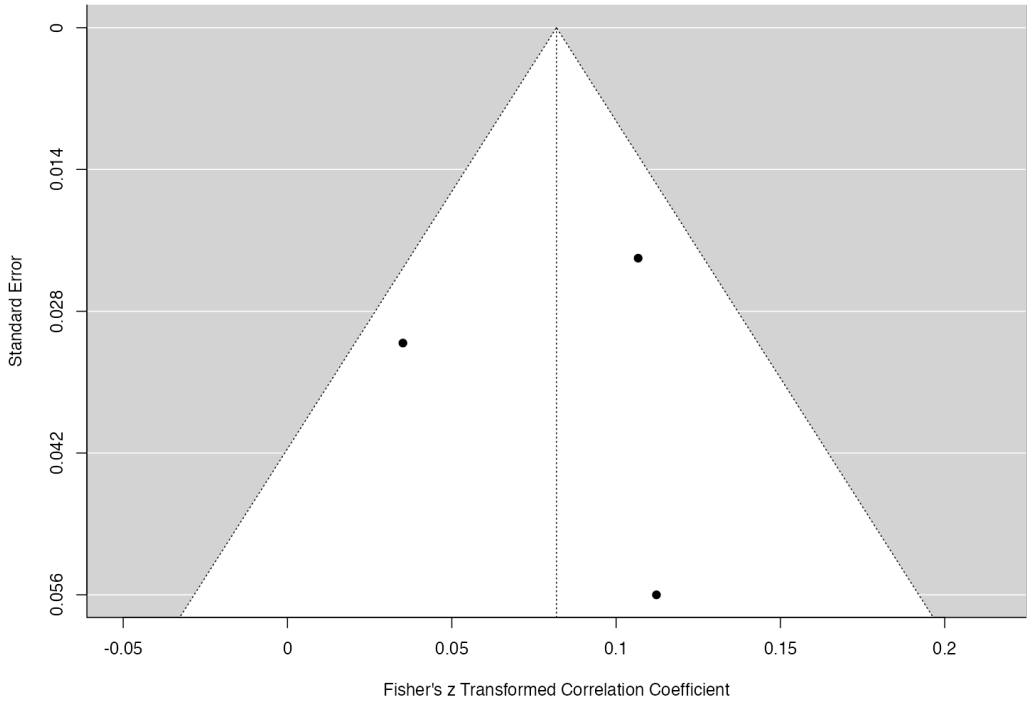


Figure C2.

Funnel plot of correlation coefficient estimates of antidepressant use

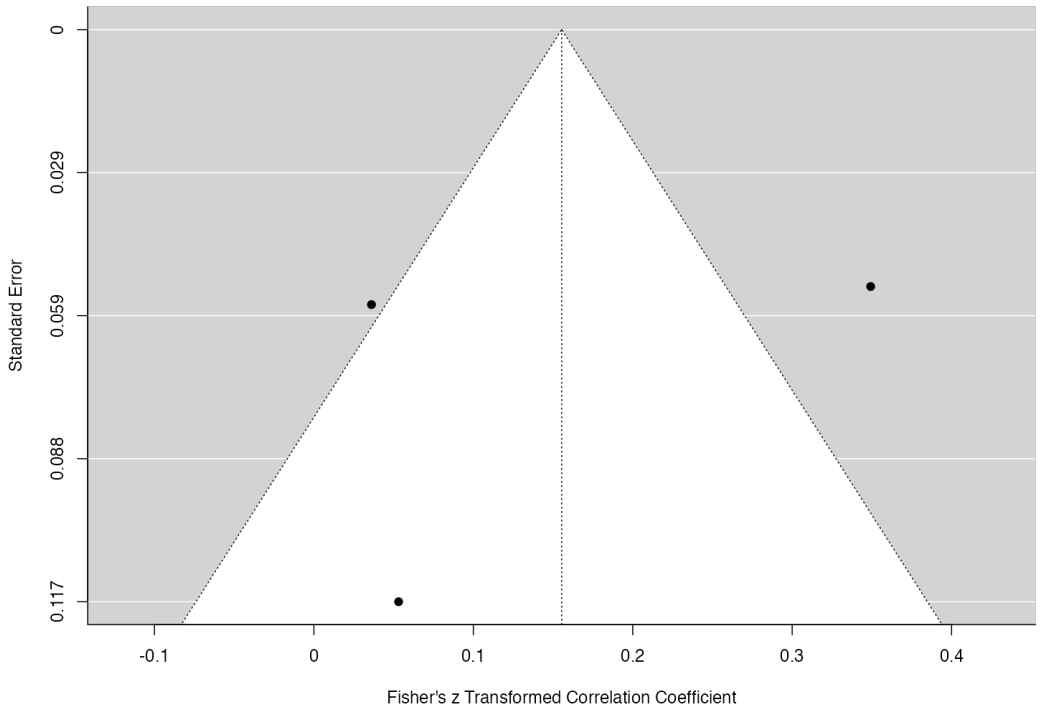


Figure C3.

Funnel plot of correlation coefficient estimates of prescription opioid use

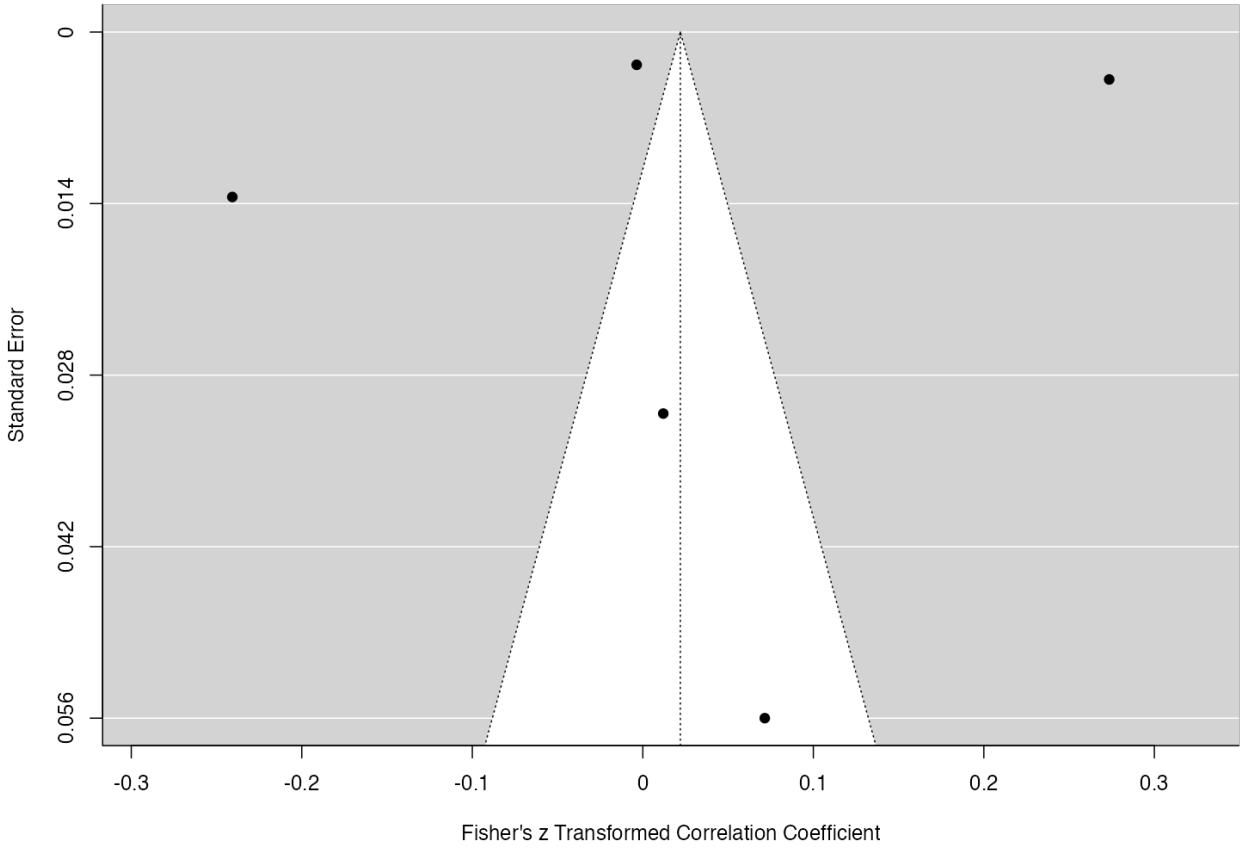


Figure C4.

Funnel plot of prevalence estimates of psychotropic prescription drug use

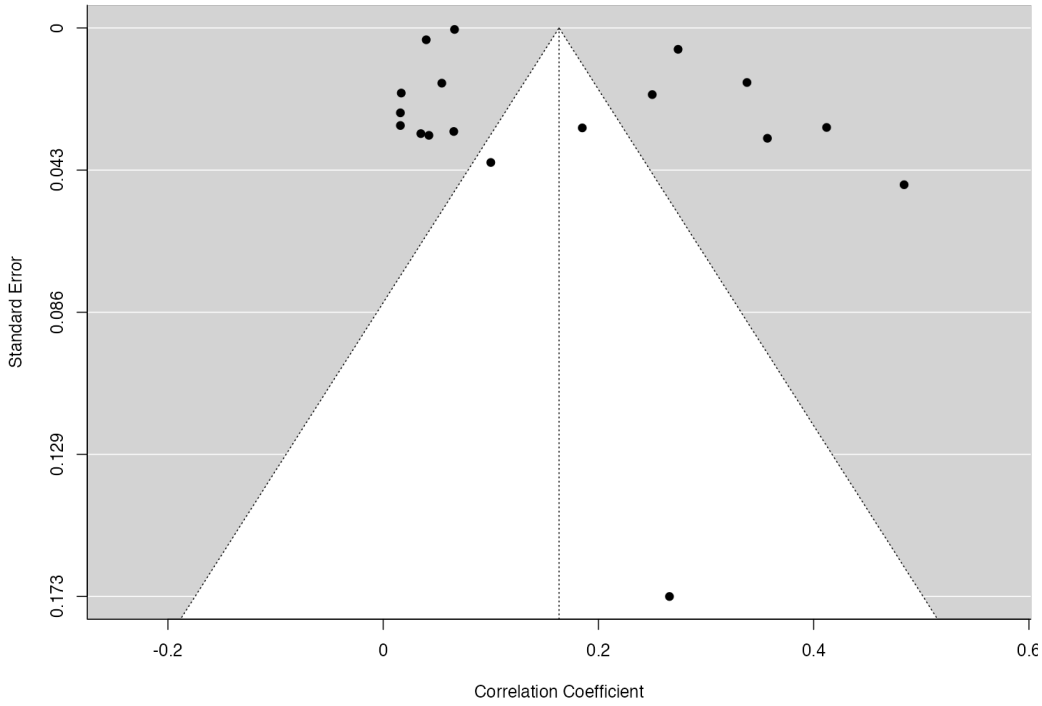


Figure C5.

Funnel plot of prevalence estimates of psychotropic prescription drug use as function of gender distribution

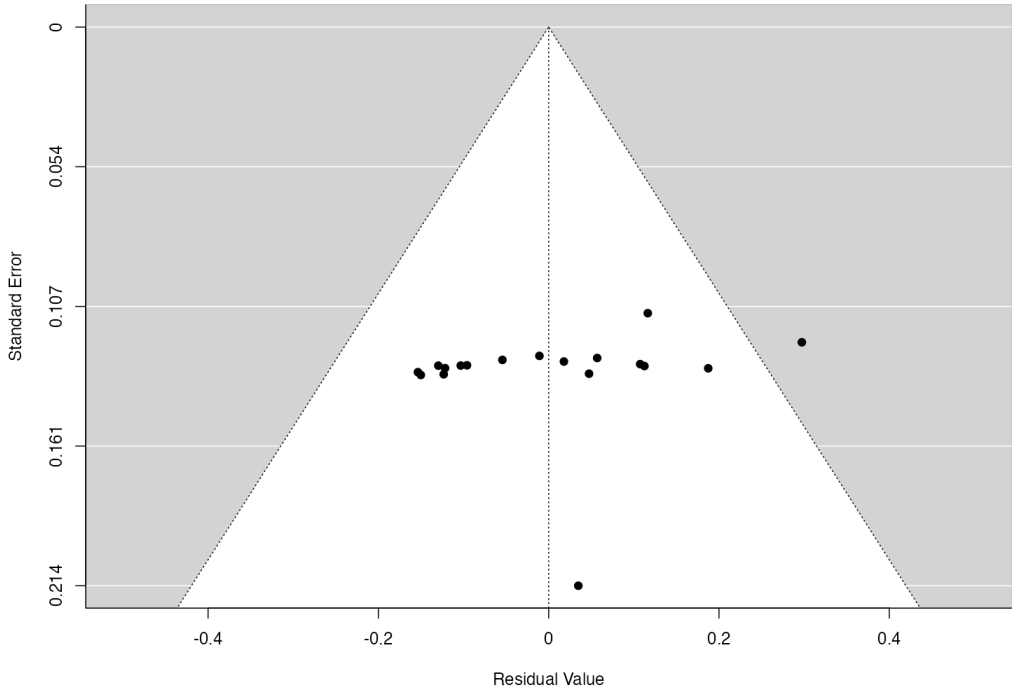


Figure C6.

Funnel plot of prevalence estimates of central nervous system depressant use

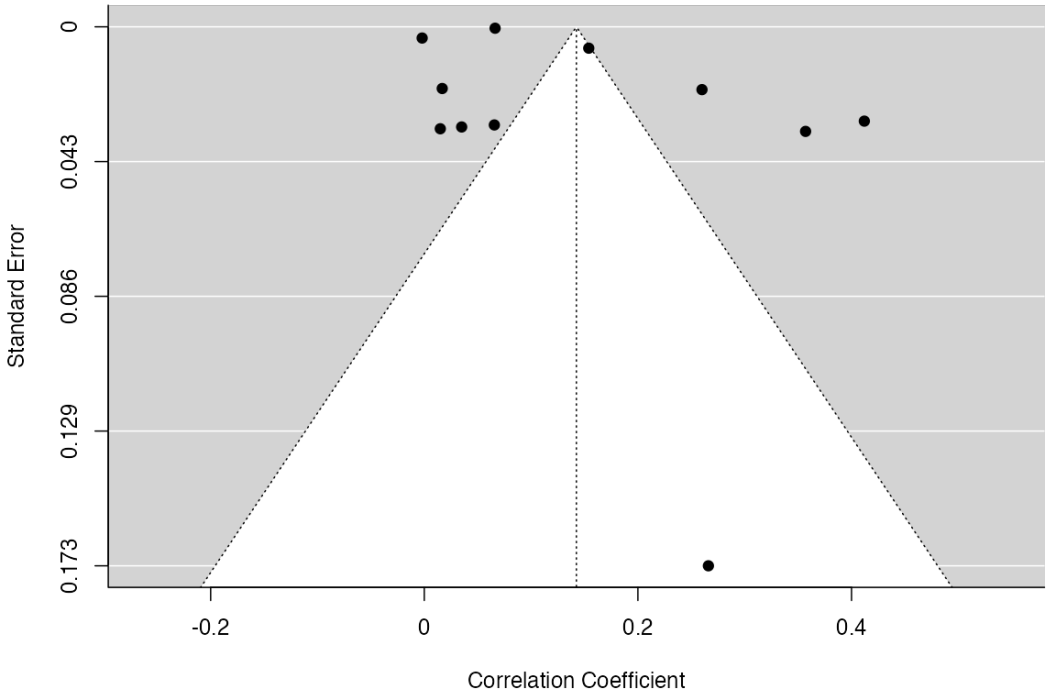


Figure C7.

Funnel plot of CNS depressant use as function of gender distribution

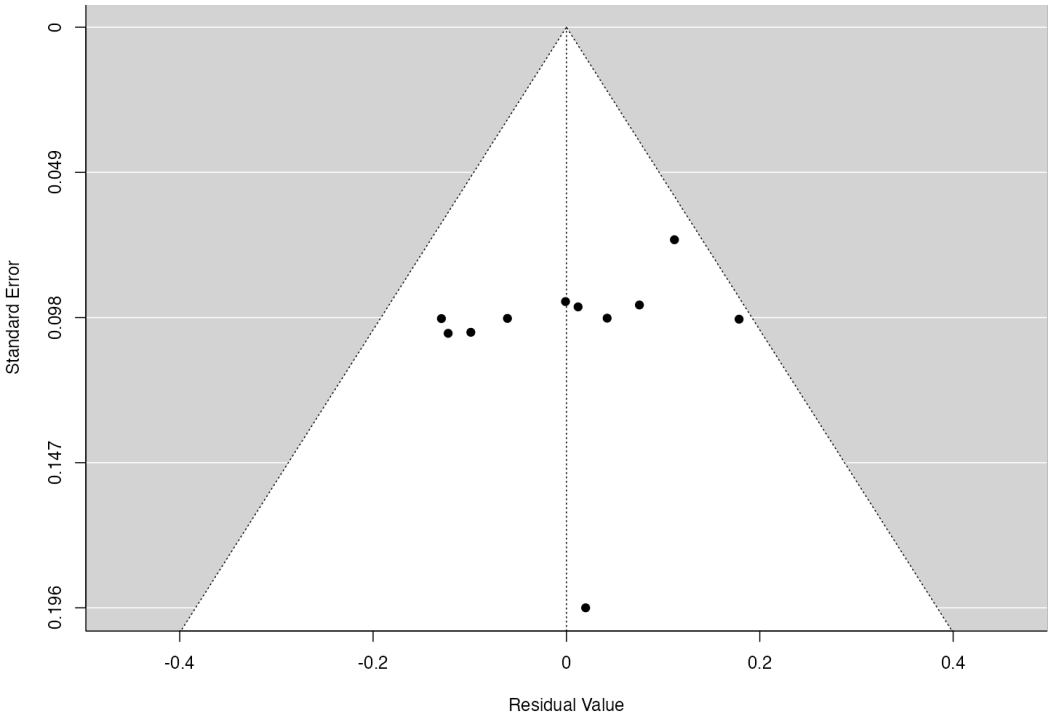


Figure C8.

Funnel plot of prescription opioid use

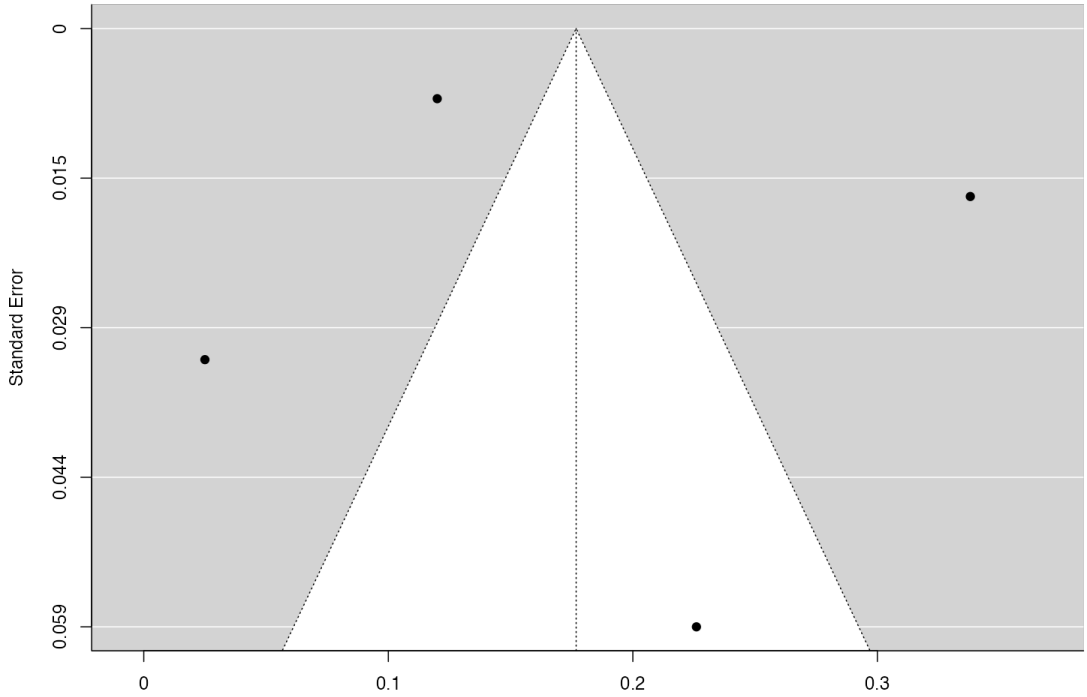


Figure C9.

Funnel plot of prescription opioid use by function of continent

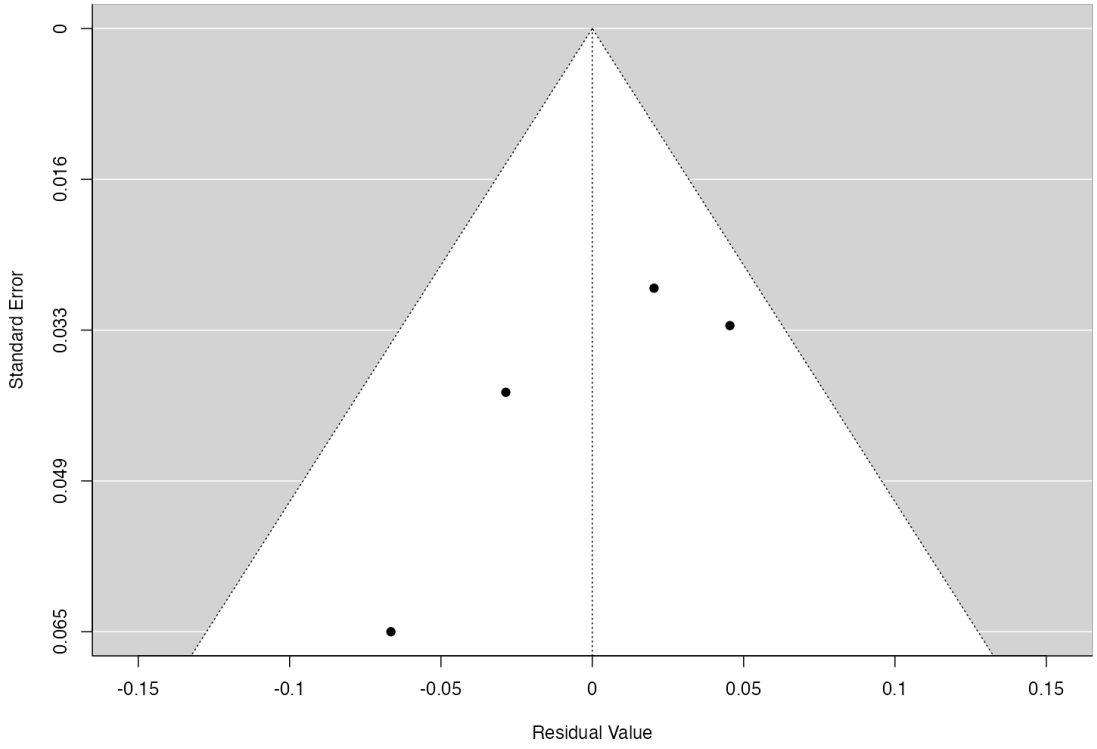


Figure C10.

Funnel plot of correlation coefficient estimates of psychotropic prescription drug use