Prevalence of comorbidities of substance use disorders with anxiety disorders and post-traumatic stress disorder in people seeking treatment for substance use: a systematic review protocol

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ABSTRACT

Objective: This systematic review will aim to assess evidence of the prevalence of the comorbidities of substance use disorders with anxiety disorders and post-traumatic stress disorder in people seeking treatment for substance use.

Introduction: Research shows that anxiety disorders and post-traumatic stress disorder are highly prevalent in people with substance use disorders and can worsen the treatment outcomes, increasing the risk for relapse and poor adherence. However, evidence from systematic reviews on the prevalence of these comorbidities in substance use treatment settings is limited.

Inclusion criteria: Participants will be people seeking treatment for substance use. Studies will be included if they have investigated the prevalence of the comorbidities of substance use disorders with anxiety disorders and post-traumatic stress disorder in treatment settings.

Methods: Primary studies will be screened from the databases MEDLINE (PubMed), PsycINFO, CINAHL, and Embase, and from searches to source gray literature. Eligible cross-sectional and cohort studies will be retrieved, and their methodological quality will be assessed. Data extraction will include study details, methods, and outcomes. Results will be described by narrative summary or, if studies are sufficiently similar, a meta-analysis will be performed. Prevalence data will be pooled for meta-analysis by a random effects model. The results will be presented graphically in a forest plot. Data heterogeneity will be statistically tested using $\chi^2$ and $I^2$ tests. If substantial heterogeneity is detected, sources of heterogeneity will be explored by subgroup analysis and meta-regression, and results will be presented by a narrative summary.

Systematic review registration: PROSPERO CRD42020149956

Keywords: anxiety disorder; post-traumatic stress disorder; prevalence; substance use disorder; systematic review


Introduction

Mental health and substance use disorders have been the leading causes of the non-fatal disease burden worldwide, reflecting a lack of significant improvement in the mental health of the world’s population.¹ Substance use disorders consist of cognitive, behavioral, and physiological symptoms caused by the continuous use of one or more substances by an individual, despite the significant problems generated by their use.² Some negative consequences for these disorders are risky use, low control, and social deterioration.² Drug classes that are involved in substance use disorders include alcohol, cannabis, hallucinogens, inhalants, opioids, sedatives, hypnotics or anxiolytics, stimulants, tobacco, and other or unknown substances.²

The occurrence of other mental disorders that are either pre-existing or emerge during the clinical course of a substance use disorder characterizes a
comorbidity, also referred to as dual diagnosis or co-occurring disorder. This comorbidity is common for substance users, strongly related to the severity of mental disorders, and may contribute to the high burden of mental and substance use disorders.

Comorbidity between substance use disorder and other mental disorders may be the result of a shared vulnerability to two or more independent conditions, or there may be a causal relationship between them. For example, substances used as self-medication for anxiety relief may lead to the development of substance use disorder or, conversely, substance use can trigger a psychiatric disorder running an independent course. In addition, there is a risk of a temporary disorder occurrence known as substance-induced disorder, developed during or shortly after intoxication or withdrawal from substance or medication.

The treatment and clinical evolution of the substance user is usually negatively influenced by comorbid mental disorders, given that one disorder leads to maintenance of the other. These comorbidities have a significant impact on the psychosocial functioning and quality of life of these patients, making treatment challenging. Knowing the prevalence of the comorbidities is one of the first steps toward a truly effective treatment in the area of substance use disorders.

As substance use disorder is complex, affecting the physical, psychological, and social well-being of each patient individually, therapeutic approaches must also be tailored for each individual, depending on their needs. In general, treatments include motivational and behavioral interventions, relapse prevention, medical and pharmacotherapy, and social approaches. There are different treatment settings for substance use disorders, such as general outpatient services, substitution treatments, withdrawal care for detoxification, and residential rehabilitation.

Studies assessing clinical samples reported a high level of comorbidity between substance abuse and mental disorders, with anxiety, mood, and personality disorders being the most common. Out of these, anxiety disorders have received less attention in studies assessing substance use disorders treatment outcomes. However, anxiety disorders modify the presentation and treatment of substance use disorders and may increase the risk for relapse and poor outcomes. Post-traumatic stress disorder (PTSD), which was considered as anxiety disorder by the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), is associated with more severe symptoms and greater resistance to treatment. The new classification of mental disorders (DSM-V) excluded PTSD from the classification of anxiety disorders, along with a significant change in its diagnostic criteria, as presented in the chapter on trauma and stressor-related disorders of the DSM-V. Another change in the DSM-V was that panic disorder and agoraphobia became independent disorders.

A preliminary search for systematic reviews or protocols in PROSPERO, Cochrane Library, MEDLINE (PubMed), and JBI Evidence Synthesis and JBI Systematic Review Register retrieved three systematic reviews assessing the prevalence of comorbid anxiety disorders with substance use in treatment settings. Post-traumatic stress disorder was included as an anxiety disorder in these studies, which used DSM-IV criteria. They confirmed a high prevalence of these disorders among substance abuse treatment patients. One of these reviews was restricted to Australia; the others were restricted to one type of substance.

To the best of our knowledge, there is no published or in-progress systematic reviews assessing comorbidities of substance use disorders with anxiety disorders and PTSD, specifically in treatment settings, not restricted to a country or one specific substance. The differences in prevalence due to the types of substances are not clear, nor whether the prevalence rates can be affected by changes in the diagnostic criteria of DSM-V in relation to the previous edition, DSM-IV.

Study of the occurrence of anxiety disorders and PTSD in treatment settings for substance use disorders can help to improve the coverage of adequate treatment. Furthermore, understanding the complexities of these comorbidities is relevant for planning successful prevention approaches.

Thus, this systematic review aims to assess the quantitative evidence of the prevalence of the comorbidities of substance use disorders with anxiety disorders and PTSD in people seeking treatment for substance use disorders.

**Review questions**

i) What is the prevalence of comorbidities of substance use disorders with anxiety disorders and PTSD in people seeking treatment for substance use disorders?
ii) Are there differences in the prevalence of comorbidities of substance use disorders with anxiety disorders and PTSD among subgroups of people seeking treatment for substance use disorders, categorized by sex (men vs women), types of substances (alcohol, prescribed drugs, other drugs), classification of mental disorders (DSM-IV or V), and treatment setting (inpatient vs outpatient)?

**Inclusion criteria**

**Participants**

Included studies must have assessed adolescents (aged 10 to 19) or adults (aged over 19) of both sexes seeking treatment for substance use disorders, including psychosocial (e.g., cognitive-behavioral therapy or contingency management) and pharmacotherapy interventions. All substances related to substance use disorder will be considered.

**Condition**

Studies will be included if they have investigated the prevalence of comorbidities of substance use disorders with anxiety disorders and PTSD, and have reported prevalence estimates or data that allow prevalence to be assessed in their sample. Included studies must have defined their diagnoses based on the diagnostic criteria of DSM IV\(^1\) and DSM V\(^2\) and must have used validated diagnostic instruments.

Studies reporting prevalence rates using screening instruments will be excluded. Studies reporting prevalence rates for substance use disorder separately from the other analyzed disorders (anxiety disorders or PTSD) will be excluded. Comorbid disorders not independent, but induced by substance/medication or other medical conditions will not be considered. The DSM IV and DSM V enables differentiating substance-induced from independent disorders by searching the chronological relationship between intoxication or withdrawal and the anxiety syndrome.\(^2,18\) Anxiety disorder due to another medical condition, for example cardiovascular disorders, is diagnosed when the medical condition induced and preceded its onset.\(^2,18\)

Studies reporting presence of other comorbidities or previous treatment for substance use disorder will not be excluded.

We will individually extract and analyze PTSD and any specific anxiety disorder (panic disorder, agoraphobia, generalized anxiety disorder, specific phobia, social anxiety disorder, separation anxiety disorder, selective mutism). Specific anxiety disorders will also be analyzed as a group.

**Context**

Studies carried out in treatment settings for substance use disorders from any location will be considered, and will include both outpatient and inpatient settings, such as those involving general outpatient services, substitution treatments, withdrawal care for detoxification, and residential rehabilitation.

**Types of studies**

Cross-sectional and cohort studies will be considered with no restriction on the language.

**Methods**

This systematic review will follow the JBI methodology for conducting the review and synthesis of prevalence studies.\(^23\) This protocol has been registered in PROSPERO (CRD42020149956), and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P) guidelines.\(^24,25\)

**Search strategy**

The search strategy will initially be developed using the key terms or concepts of the review question in a logical grid.\(^26\) As it is a systematic review of prevalence, this logic grid will contain tree columns representing the condition, the population, and the type of the studies. The key terms that have been identified in the review questions are anxiety disorders and PTSD (as conditions); substance use disorder (as population); and prevalence (as type of studies). A three-step search strategy will be followed: i) preliminary search; ii) structured search; and iii) manual search.

A preliminary search (first step) was conducted in MEDLINE (PubMed) using the key terms identified from the logic grid. This search aimed to identify the MeSH terms and find corresponding terms or synonyms for the key terms. The MeSH terms also provided the “entry terms” and other related terms that could be useful to the search, along with additional “free terms” chosen by the authors. The results of this first step guided the development of a structured search strategy (second step) also performed in MEDLINE (PubMed).
The search strategy was limited to studies published after 1994, when the DSM-IV was launched. Results of this structured search in MEDLINE (PubMed) are shown in Appendix I. The quality of the first search strategy was tested and confirmed independently by two reviewers after an initial screening of titles and abstracts of 20% of the total number of studies found.

Gray literature will be searched using similar keywords to those defined by the structured search. After identifying eligible studies, their reference lists will be used to manually search for additional studies (third step).

The databases to be searched are MEDLINE (PubMed), PsycINFO (APA PsycNet), CINAHL (EBSCOhost), and Embase (Elsevier). Google Scholar and ProQuest Dissertations and Theses will be searched for gray literature. Authors of included studies that have unpublished data of interest to this systematic review will be contacted by email to provide additional information.

Study selection
The study selection process will be performed using EndNote v.X7 (Clarivate Analytics, PA, USA) and Excel (Redmond, Washington, USA) worksheets developed by the reviewers. The identified studies will be uploaded into EndNote and duplicate citations will be removed. The selection of studies will then continue in two stages. First, two reviewers will independently screen the titles and abstracts according to the eligibility criteria to identify studies for full text retrieval. Studies will also be retrieved in full where suitability is uncertain. Second, the reviewers will independently read the full texts, identifying articles to be included. Disagreements will be discussed and, if necessary, a third author will be consulted. Full text studies that do not meet the inclusion criteria will be excluded, and the reasons for these exclusions will be provided in the final systematic review report. The results of this selection will be presented in a PRISMA flow diagram.

Assessment of methodological quality
After selection, two independent reviewers will critically appraise the methodological quality of the included studies using the JBI critical appraisal tool. This information will be reported and used to interpret the results in the final review document. Disagreements regarding methodological quality assessment will be discussed and, if needed, a third reviewer will be consulted for a decision. Regardless of the results of methodological quality assessment, all included studies will undergo data extraction and synthesis.

Data extraction
Two reviewers will independently extract data from the included studies using the JBI standardized data extraction tool for prevalence and incidence adapted for this systematic review (Appendix II). Disagreements regarding the study details to be extracted will be resolved by discussion or, if necessary, by a third reviewer. Data extraction will include the following information: i) publication and study details; ii) study methods, and iii) results (proportion of substance users reported with last month, last year, or lifetime prevalence of anxiety disorders and PTSD). Prevalence data will be retrieved for each substance target if they have been assessed separately. In order to provide missing or additional data, authors of the primary studies will be contacted by email. Where missing outcome data cannot be obtained, and data imputation cannot be performed, the studies will be excluded for the outcome in question.

Data synthesis
Where the included studies present sufficient similarity, a meta-analysis will be performed; otherwise, the results will be described by a narrative summary including tables and figures when appropriate, and the sources of heterogeneity will be discussed. Prevalence data will be transformed by double arcsine transformation to calculate the weighted summary of proportion, and pooled for meta-analysis under a random effects model statistical assumption, using Metafor (Free Software Foundation, Inc., Boston, USA). The effect size will be expressed as a proportion with 95% confidence intervals around the summary estimate. The results will then be presented graphically in a forest plot. Data heterogeneity will be assessed statistically using $\chi^2$ and $I^2$ tests. If substantial heterogeneity is detected, sources of heterogeneity will be explored by subgroup analysis and meta-regression in order to assess the influence of
each variable on the overall heterogeneity. Subgroups will be defined according to sex (men vs women), types of substances (alcohol, prescribed drugs, other drugs), classification of mental disorders (DSM IV or DSM V), and treatment setting (inpatient vs outpatient). Meta-regression will be performed if there are a sufficient number of included studies (at least 10), and will be used to investigate whether a particular covariate may explain the heterogeneity of the outcome between studies. All statistical analyses will be achieved using R software v.3.6.1 (The R Foundation, Auckland, New Zealand). Publication bias will be verified by visual inspection of a funnel plot, constructed using sample size as the measure of accuracy on the y-axis. Differences found in the populations assessed by the individual studies, and the important discrepancies in methods and results will be described narratively.

Acknowledgments
Editage for English-language editing.

References
## Appendix I: Search strategy

**MEDLINE (PubMed)**


<table>
<thead>
<tr>
<th>Search</th>
<th>Search terms</th>
<th>Records retrieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>#3</td>
<td>Prevalence [MeSH Terms] OR prevalence [Title/Abstract] OR prevalences [Title/Abstract]</td>
<td>732,643</td>
</tr>
<tr>
<td>#4</td>
<td>#1 AND #2 AND #3</td>
<td>2918</td>
</tr>
</tbody>
</table>

Limited to date after 1994
Appendix II: Data extraction instrument

Reviewer_____________________ Date ____/____/____ Study ID________

I. Publication and studies’ details

<p>| | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>1. Study title</td>
<td></td>
</tr>
<tr>
<td>2. Author (first author)</td>
<td></td>
</tr>
<tr>
<td>3. Year of publication</td>
<td></td>
</tr>
<tr>
<td>4. Journal/source</td>
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</table>
## II. Study method

1. **Aim of the study:**

2. **Treatment setting:**

3. **Study design:**

4. **Subject characteristics**
   - **4.1 Age**
     - (mean/DP) ______ / ______
     - Categories (n):
   - **4.2 Sex (n/%)**
     - Men: _____ / _____
     - Women: _____ / _____
     - Missing: _____ / _____
   - **4.3 Country/location:** ____________________
   - **4.4 Sample size (N):** ____________________
   - **4.5 Diagnosis:** ____________________________________________
   - **4.6 Diagnostic/classification criteria for mental disorders:** ____________________
   - **4.7 Dependence severity (n)**
     - DSM-IV Abuse: ______ Dependence: ______
     - DSM-V Mild: ______ Moderate: ______ Severe: ______
   - **4.8 Other comorbidities:** ____________________
   - **4.9 Types of substance use disorders seeking treatment for:** ____________________
   - **4.10 Was there previously treatment for substance use disorder:**
     - Yes: ______
     - No: ______
   - **4.11 Receiving psychiatric medication (n)**
     - Yes: ______
     - No: ______
   - **4.12 Receiving mental health or psychiatric services in parallel (n)**
     - Yes: ______
     - No: ______

5. **Dependent variables:**

6. **Outcomes:**
   - **6.1 Primary:**
   - **6.2 Secondary (when relevant):**

7. **Outcomes measurement:**

8. **Ethical approval:**
   - Yes: ______
   - No: ______

9. **Sampling methods:**

10. **Legality of substance used:** (fulfil in table 2)

11. **Method of data analyses:**

12. **Dates of survey:**
### III. Results

**Table 1 Prevalence of comorbidity**

<table>
<thead>
<tr>
<th></th>
<th>Anxiety disorder: _______________</th>
<th>Post-traumatic stress disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>Y</td>
</tr>
<tr>
<td>(n/%)</td>
<td>95% Cl</td>
<td>(n/%)</td>
</tr>
</tbody>
</table>

M, last month; Y, last year; L, lifetime.

**Table 2 Prevalence data for substances target**

| Substance: | Prevalence of Co-occurrence (N: ____)
<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>Leg</td>
</tr>
<tr>
<td></td>
<td>(y/n)</td>
</tr>
<tr>
<td>1. Alcohol</td>
<td>n/%</td>
</tr>
<tr>
<td>2. Amphetamine</td>
<td></td>
</tr>
<tr>
<td>3. Anxiolytic</td>
<td></td>
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<tr>
<td>4. Cannabis</td>
<td></td>
</tr>
<tr>
<td>5. Cocaine</td>
<td></td>
</tr>
<tr>
<td>6. Hallucinogens</td>
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<tr>
<td>7. Heroin</td>
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<tr>
<td>8. Hypnotic</td>
<td></td>
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<tr>
<td>9. Inhalants</td>
<td></td>
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<tr>
<td>10. Morphine</td>
<td></td>
</tr>
<tr>
<td>11. Phencyclidine</td>
<td></td>
</tr>
<tr>
<td>12. Sedative</td>
<td></td>
</tr>
<tr>
<td>13. Tobacco</td>
<td></td>
</tr>
<tr>
<td>14. Others</td>
<td></td>
</tr>
<tr>
<td>15. All Substances (Not specified)</td>
<td></td>
</tr>
</tbody>
</table>

Leg, legality; M, last month; Y, last year; L, lifetime

### IV. Comments

1. Author’s comment
2. Reviewer’s comment