**The Role of Comorbidities in Opioid Overdose Risk: A Systematic Review**

**Abstract**

The opioid overdose crisis has escalated into an international public health emergency, with mortality rates continuing to rise, a trend that was further intensified during the COVID-19 pandemic. Individuals with mental health conditions such as anxiety, depression, and thought disorders are at a heightened risk of opioid overdose, yet the relationship between mental health diagnoses and opioid overdose remains poorly understood. This systematic review aims to assess existing studies that explore the link between opioid overdose risk and diagnosed mental health disorders in developed countries, including North America, Western Europe, and Australia. Following PRISMA guidelines, the review examines 28 studies investigating the prevalence of both fatal and non-fatal opioid overdoses among individuals with mental health disorders. The findings consistently reveal a positive association between mood disorders, particularly depression and anxiety, and an increased risk of opioid overdose. The bidirectional relationship between mental health issues and opioid misuse highlights the critical need for integrated treatment approaches that address both psychiatric and substance use disorders. Future research should focus on longitudinal studies and the development of dual interventions targeting mental health and opioid use disorder (OUD) prevention for at-risk populations. To effectively combat the ongoing opioid overdose crisis, comprehensive harm reduction strategies and mental health programs must be implemented in a unified manner.

KEYWORDS: anxiety, depression, opioid overdose, PRISMA,

**Introduction**

The opioid overdose pandemic has turned into an international health emergency. [1,2], with mortality rates steadily rising over time, especially so during the COVID-19 pandemic [3]. Evidence suggests that people who have co-occurring mental health disorders such as Hallmood, anxiety, or thought disorders are at a greater risk for an overdose [4–7]. Still, there is limited research on the precise relationship between mental health-related conditions and opioid overdoses; consequently, how they are intertwined remains to be clearly understood.

Studies have shown in the past that individuals with mental illnesses tend to miss out on opioids when they have them prescribed [8–12], but all kinds of factors make it hard to draw any specific conclusions. For one thing, the overlap between symptoms of substance use disorders, mental health problems, and side effects from medications can cause difficulty in seeing a clear connection [13]. Another factor is that prescription opioids or other drug use treatments might bring on more significant problems for those with mental illness: they are, per se, higher risks for overdose [14]. What's more, over time, the effect of diagnostic inflation could have recast a lot of mental health problems into drug abuse-related symptoms and criminal behavior, for which there are many complicated issues [15].

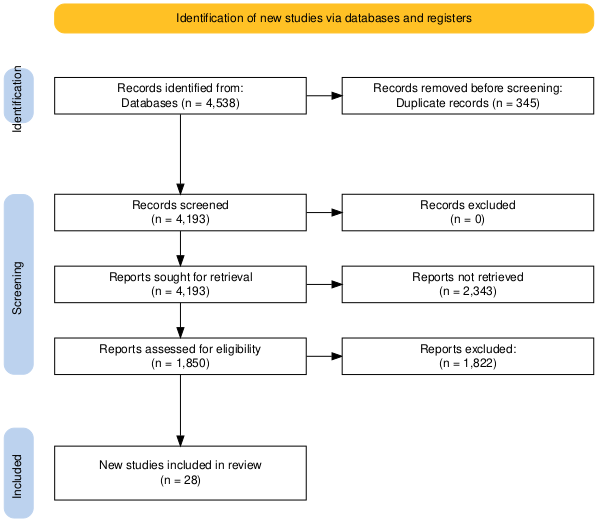
The causality related to mental health disorders and opioid overdose remains an open question. While factors such as stigma, social isolation, and the stress that comes along with opioid use might worsen mental health outcomes, opioids could equally be being used as a form of self-medication by those with dysphoria or, indeed, symptoms of mental illness [16]. Unfortunately, the direction of this relationship and its moderators have not been thoroughly studied. One possible explanation is the process of social causation, meaning that social and economic challenges lead to both drug misuse and mental health problems [17,18]. Social selection theory would indicate that mental illnesses could themselves lead to an individual's decline in social standing [19].

Although the intersection of mental health disorders with overdose by opioids is increasingly acknowledged as an essential research priority, to date, any significant analysis of this relationship remains outstanding. Gaps in knowledge still exist on the magnitude and scope of mental health disorders associated with overdose risk, as well as its underlying mechanisms [20]. This systematic review seeks to fill these lacunae by compiling current research knowledge and offering new angles for prevention opportunities for better policies on how to proceed.

**Methods**

**Search Strategy and Selection Criteria**

A systematic review was conducted following the PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines [21]. All these reviews specifically searched for studies published in English from peer-reviewed journals or government reports between January 1, 2000, to January 3, 2023. The focus was on research in America, Europe, the United Kingdom, Australia, and New Zealand to ensure high contextualisation and policy relevance as preferred by stakeholders. There were also three stages in the searching process, using subject headings and keywords to search the relevant literature. Appendix A provides a detailed breakdown of search terms used in the Medline database. Additional searches utilized grey literature platforms like Open Grey or conference proceedings, and experts were contacted for unpublished studies. The review question was framed using the PECOS (Population, Exposure, Comparison, Outcome, Study Design) model, focusing on the relationship between mental health issues and opioid overdose.



**Figure 1: Prisma Flowchart**

**Data Collection and Extraction**

Two independent research assistants used a standardized form to extract data. The fields extracted included publication year, location, study design, sample size, measures of mental disorders, and outcomes from opioid overdose. Two reviewers checked the data for consistency, and any discrepancies were discussed with a senior researcher.

**Study Selection and Data Synthesis**

The initial search retrieved 4538 records, of which 28 satisfied the inclusion criteria. These were analyzed and synthesized using the lumping technique, which combines studies that examine comparable variables and outcomes. Risk of bias assessments for each study were also made.

**Table 1. Search Strategy**

|  |  |
| --- | --- |
| **Concept** | **Search Terms** |
| **Mental Health** | Mental health; psychiatric illness; mental disease; treatment access; support availability; hopelessness, suffering and pain crisis code calls Related: Disability and Vulnerability Stigma Code-calls for social isolation & elopement Marginalization |
| **Overdose** | Overdosing, deaths due to overdose, side effects, pharmacological toxicity |
| **Opioids** | People with opioid (medical/non-medical) use disorder prescribed opioids; people with opioid use disorder oral or injection |
| **Databases** | MEDLINE (Ovid), Embase (Ovid), PsycINFO (EBSCOhost), CINAHL (EBSCOhost), Google Scholar Cochrane Central Registry of Controlled Trials(CENTRAL), Cochrane Drug and Alcohol Group (CDAG), Specialised Register |
| **Other Sources** | Grey literature platforms (e.g., OpenGrey), conference proceedings, expert consultations |
| **PECOS Criteria** | **Population**: People using opioids in North America, Europe, the UK, Australia, and New Zealand.  **Exposure**: Any measure of mental health (e.g., psychiatric disorder, psychological distress).  **Comparison**: Quantitative studies comparing groups with varying mental health levels.  **Outcome**: Opioid-related fatal and non-fatal overdose.  **Study Design**: Quantitative studies with empirical data (case reports, reviews, editorials excluded). |

**Data Collection and Extraction**

Data collection followed a systematic procedure to ensure precision and reliability. Data extraction and extracted data from eligible studies using a standardized and pilot-tested form. In its collection form, the researchers process various types of information from the studies: publication year, journal source, author details, geographic location, study design (cross-sectional or longitudinal), population size, and representation (excluding patients with a mandatory date of response/willingness to participate); possibility to generalize findings based on definitions for excluded study populations if indicated), recruitment method and sampling infrastructure; response rates; season of data collection. In each study, specific information about the operationalization of mental health disorders (e.g., diagnosed psychiatric disorders, self-reported symptoms), opioid overdose (fatal and non-fatal) type, and relevant statistical analyses were meticulously noted as well [22].

These two research assistants independently extracted data from the studies to guarantee reliability. Their results were cross-referenced against each other post-extraction. These were reviewed, and when inconsistencies or disagreements arose, these were discussed with a senior researcher, and a consensus was reached about the final extracted data. This process reduced mistakes and increased the quality of the data collection phase, an essential requirement in systematic reviewing as it ensures that high standards are met regarding both integrity and reliability [20,23].

In addition, important data regarding the studies (e.g., how mental disorders were defined [clinical diagnoses, self-reported symptoms, etc.] and related outcomes to opioid overdose) needed to be extracted. In addition, details on the overdose type (fatal vs. non-fatal; intentional vs. unintentional) were fully extracted to allow in-depth exploration of the association between mental health comorbidities and opioid overdose. Studies that considered multiple types of overdoses or different levels/degrees of mental health were given particular attention to ensuring the richness of these constructs was captured [24].

Risk of bias assessments should always be made for each included study because they are needed to maintain correctness and consistency throughout the results. We used tools provided by the National Heart, Lung, and Blood Institute to assess the risk of bias about several domains, including study design, recruitment of participants, measurement techniques, and statistical analyses [25,26]. The same two reviewers independently conducted this assessment as well. These ratings allowed the researchers to compare lopsided biases in each study and control for them when combining the results. This step was imperative in assessing the quality of the evidence base, as studies with higher bias scores would differentially contribute to data synthesis and interpretation.

The Review Team created a robust dataset based on systematic and validated data extraction and risk of bias assessment. The extraction process allowed for thorough vetting of the data collected in this phase of synthesis, which was important because it resulted in a reliable and all-inclusive dataset that facilitated critical analysis and synthesis of mental health disorder—and opioid overdose-related outcomes.

**Table 2. Characteristics of Included Studies**

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| --- | --- | --- | --- | --- | --- |
| **First Author (Year)** | **Study Design/Location** | **Sample Characteristics** | **Mental Disorder Measure** | **Opioid Overdose Characteristics** | **Key Findings** |
| Bohnert et al. [26,27] | Case-cohort/USA | N=155,434; Age: 18–59 years; 93.3% male | Any mental disorder | Prescription opioids: Unintentional, fatal | Mental disorders linked to overdose in chronic pain populations but not cancer patients. |
| Burns et al. [27] | Cross-sectional/Australia | N=163; Median age: 21; 54.0% male | Hopelessness, mental illness, self-harm, depression | Non-prescription opioids; Non-fatal | Hopelessness and antisocial behavior associated with overdose risk. No significant association with depression. |
| Campbell et al.[28] | Cohort/USA | N=396,452; Mean age: 51.83 years; 41.0% male | Mood/anxiety disorders | Prescription opioids: Fatal and non-fatal | Mood/anxiety disorders linked with increased overdose risk. |
| Carrà et al. [29] | Cross-sectional/Italy | N=265; Mean age: 35.4 years; 79.0% male | Suicidality | Non-prescription opioids; Non-fatal | There is no significant association between suicide attempts and overdose risk. |
| Chahua et al. [30,31] | Cohort/Spain | N=452; Mean age: 26 years; 27% male | Depression | Prescription/non-prescription opioids; Non-fatal | Depression is associated with a higher risk of overdose (AOR 2.2). |
| Cheng et al. [31] | Cross-sectional/USA | N=254; Age range: 18-44 years; 57.5% male | Any mental disorder | Prescription/non-prescription opioids; Fatal | Mental disorders are linked to unintentional fatal opioid overdoses. |
| Dunn et al. [32] | Cohort/USA | N=9,940; Mean age: 54 years; 40.4% male | Anxiety, depression | Prescription opioids: Fatal and non-fatal | Depression and anxiety are significantly linked to higher opioid overdose risk. |
| Chua et al. [33] | Cohort/USA | N=2,752,612; Mean age: 17.2 years; 47.2% male | Mood disorders | Prescription opioids; Non-fatal | Mood disorders associated with opioid overdose (AHR 2.3). |
| Darke et al. [15] | Cross-sectional/Australia | N=615; Mean age: 29.3 years; 66.0% male | Depression, hopelessness | Non-prescription opioids; Non-fatal | Depression associated with non-fatal overdose risk. |
| Fendrich et al. [34] | Cohort/USA | N=368; Mean age: 35 years; 72.3% male | Depression | Prescription opioids; Non-fatal | Depression is associated with a higher risk of opioid overdose. |
| Kline et al. [35] | Cross-sectional/USA | N=487; Mean age: 27 years; 55.3% male | Any psychiatric disorder | Prescription opioids: Unintentional, fatal | Psychiatric disorders were significant risk factors for opioid overdose in multiple subpopulations. |
| Maloney et al. [36] | Cross-sectional/Australia | N=582; Age range: 20–35 years; 50.8% male | Anxiety, depression | Prescription opioids: Fatal | Anxiety and depression are linked to a higher risk of opioid overdose in younger adults. |
| Mazereeuw et al. [37] | Case-control/Canada | N=59,784; Age: 35–59 years; 45.6% male | Anxiety, depression, mood disorders | Prescription opioids: Fatal and non-fatal | Mood disorders, particularly depression, are strongly associated with fatal overdoses. |
| Lagisetty et al. [38] | Cohort/USA | N=7,845; Mean age: 42.5 years; 60.4% male | PTSD, anxiety | Prescription opioids: Fatal | PTSD and anxiety were major contributors to overdose among veterans. |
| Karmali et al. [39] | Cohort/USA | N=1,982; Mean age: 39 years; 47.8% male | Bipolar disorder, anxiety | Non-prescription opioids; Non-fatal | Bipolar disorder is significantly associated with a higher overdose risk. |
| Peterson et al. [40] | Cross-sectional/USA | N=61,170; Mean age: 46.8 years; 49.9% male | Depression, PTSD, anxiety | Non-prescription opioids; Fatal and non-fatal | Depression and PTSD are major risk factors for opioid overdose. |
| Zedler et al. [41] | Case-control/USA | N=8,987; Median age: 62 years; 92.1% male | Mood disorders, PTSD | Prescription opioids: Fatal | Mood disorders and PTSD are strongly correlated with opioid overdose fatalities. |
| Follman et al. [42] | Cohort/USA | N=138,108; Mean age: 43.4 years; 52.4% male | Depression | Prescription opioids; Non-fatal | Depression is linked with increased non-fatal opioid overdose risk. |
| Hartung et al. [43] | Case-control/USA | N=3,508; Age: ≥30 years; 50.3% male | Depression, anxiety | Prescription opioids: Fatal | Depression and anxiety are linked to higher fatal opioid overdose risk. |
| Yoon et al. [44] | Cross-sectional/USA | N=6,686,905; Age: 12+ years | Depression, PTSD, mood disorders | Prescription opioids; Non-fatal | Mood disorders and PTSD significantly associated with non-fatal overdose. |
| Hasegawa et al. [45] | Cohort/USA | N=19,709; Median age: 42 years; 43.0% male | Depression, mood disorders | Prescription opioids; Non-fatal | Mood disorders strongly correlated with increased non-fatal overdose risk. |
| Madadi et al. [46] | Cross-sectional/Canada | N=1,359; Median age: 44 years; 61.8% male | Depression | Prescription opioids; Fatal and non-fatal | Depression linked with increased opioid overdose risk, especially in younger populations. |
| Roxburgh et al. [47] | Panel data/Australia | N=1,437; Age: 14-39 years; 50.1% male | Depression, PTSD | Non-prescription opioids; Fatal | PTSD and depression associated with fatal opioid overdose. |
| Schillinger et al. [48] | Cohort/USA | N=169,206; Age: 35+ years | Depression, anxiety | Prescription opioids; Fatal | Depression and anxiety strongly linked to fatal opioid overdose. |
| Connery et al. [49] | Cross-sectional/USA | N=120; Mean age: 34 years; 59% male | Depression | Non-prescription opioids; Non-fatal | Depression associated with increased risk of non-fatal overdose. |
| Gerhart et al. [50] | Ecological/USA | N=NR | Anxiety, depression, PTSD | Prescription opioids; Non-fatal | Anxiety, depression, and PTSD associated with increased non-fatal overdose risk. |
| Smolina et al. [51] | Case-control/Canada | N=59,784; Age: Median 39 years; 67.0% male | Depression | Prescription opioids; Non-fatal | Depression strongly associated with non-fatal overdose risk. |
| Cochrane et al. [52] | Cohort/USA | N=297,634; Age: 18-64 years | Depression | Prescription opioids; Non-fatal | Depression linked with higher risk of opioid overdose. |

**Result**

**Overall Findings**

The review process yielded 4,538 studies that first met the inclusion criteria. A total of 28 studies met the inclusion criteria for this review after screening and evaluation, which mainly aimed to investigate the relationship between mental health disorders and opioid overdose. These studies used both fatal and non-fatal overdose outcomes in multiple types of locations. Studies on fatal opioid overdoses by various categories included n=9, and studies about non-fatal events exclusively included n=14. Considering the combined fatal and non-fatal overdoses, 5 studies were conducted, and two utilizing emergency department data made no distinction between fatal or nonfatal outcomes.

**Study Designs**

Of the 28 studies included, most were conducted in the US (19 studies) followed by Australia, Canada, Italy, and Spain. Table 1: Structure of included studies, stratified according to study design (cross-sectional [10 studies], cohort [12], case-control [4], ecological analysis [2] and panel data/case-cohort type designs. Many of the studies used observational data and were unable to assess causality, but they do provide valuable findings about tionshi furtherp between mental health and overdose risk.

**Mental Health Disturbances:**

Mental health disorders were grouped into broad categories such as internalizing disorders (depression, anxiety), externalizing disorders (ADHD, personality disorders), and thought disorders (schizophrenia). Of the 24 mood studies, 17 showed a statistically significant positive association between mood disorders and opioid overdose.

**Mood and Anxiety Disorders**

In these studies, smartphones were associated with differences in risk of opioid overdose (AORs between 1.26 to 2.71) among people who had mood disorders compared with those who did not, especially depression and anxiety [26,31,53]. In contrast, four studies did not observe a significant association in veteran and Medicare populations, implying a demographically heterogeneous effect [34–36,38,45,49].

**Thought Disorders and Externalization**

Five studies examined the association between externalizing disorders and overdose, four of which reported a positive association, especially between antisocial personality disorder and overdose. On the other hand, research on thought disorders, including Schizophrenia, was inconsistent or only partially validated, with some studies reporting positive associations and others lacking significant correlations [15,27,51,54].

**Discussion**

The present systematic review reveals the complex association between mental health pathology and opioid overdoses. Virtually all of the studies included in this review reported some evidence for a positive relationship between one or more mental health outcomes and an increased risk of opioid overdose (fatal or non-fatal). The most substantial evidence came for mood disorders, particularly depression and anxiety, which had the most consistent associations with overall opioid overdose. This is consistent with previous work that indicates individuals may use opioids as a form of self-medication for internalizing mental health disorders, such as depression, and unintentionally increase their likelihood of experiencing an overdose [8,10–12,55]. Although the specific mechanisms are unknown, it is conceivable that those trying to address mental health issues are also at risk for opioid abuse in part due to the additive effects of psychiatric symptoms and substance use.

The results on anxiety disorders, also a common feature of opioid overdoses, are analogous to those seen in mood disorders as well. Anxiety is frequently comorbid with SUDs, i.e., a person with high anxiety symptoms is more likely to use opioids to receive the benefit of some relief from those unpleasant sensations. However, this increases opioid misuse and the opportunity for overdose as individual attempt to seek psychological relief through using opioids. Opioid use can worsen anxiety, which might then entice individuals to take more opioids, contributing to an increased dependence or risk for overdose.

Moderate evidence also supported an association between opioid overdose and schizophrenia/bipolar (thought disorder). There are fewer studies on these disorders but the available evidence indicates that thought disordered persons have a different flavor of opioid misuse. Those with thought disorders could be at even greater risk given that they suffer from cognitive impairments and social disconnection, which increases their likelihood of engaging in risky behaviors such as substance misuse that can cause overdose [16]. That makes those with thought disorders even more prone to overdose because they are already going without care.

**Pathways of Effects and Theoretical Thoughts**

Teasing apart the directionality of the link between mental health disorders and opioid overdose is a difficult puzzle. Mental health disorders are certainly associated with a greater risk of overdose, but it is an open question whether these psychiatric conditions cause people to use opioids or if opioid usage exacerbates or can trigger mental health conditions. One possible explanation is that opioids are being utilized as self-medication to treat mental health symptoms (e.g., depression and anxiety), which then worsen dependence and overdose risk [16]. Alternatively, chronic opioid use may causally lead to such neurochemical changes exacerbating underlying psychiatric symptomatology suggestive of a vicious cycle.

Models of social causation, however, equally invoke the association between social determinants such as poverty, unemployment and loneliness which both opioids use (particularly dependence) and mental health disorders; thereby affording a pathway by which significantly higher rates of overdose might be explained [17,18]. This common cause hypothesis is also supported by the fact that social exclusion and economic precarity are risk factors for both mental health disorders as well as substance use.

On the other hand, the social drift theory suggests that mental health problems lead to a low socio-economic position and subsequently to substance abuse, including opioid misuse for relief. [56]. The theory is particularly relevant for those with more severe mental health disorders like schizophrenia that leads to cognitive impairments and social isolation, predisposing towards unemployment and loss of social support [53] making them at great risk for substance use/overdose.

Widening the lens to these theoretical frameworks indicate that the relationship between mental health disorders and opioid overdose is complex, multifactorial, and constantly evolving. Given the complexity of these relations, it is unlikely that a single causal pathway can fully account for all [57]. Instead, various factors (e.g., psychological symptoms, social and economic circumstances) intersect to produce the outcomes. This complexity highlights the importance of interventions aimed at both psychological and social determinants of opioid overdose risk.

**Discussion: Clinical and Policy Implications**

Implications for clinical practice and public health policy According to clinical practice, this type of integrated care model would be beneficial in treating these co-occurring disorders [18]. People with co-occurring mental health and substance abuse disorders often experience fragmented care systems in which their conditions are treated separately. There is a high risk of opioid overdose with mental health and substance use treatment would reduce the burden by delivering comprehensive care that addresses psychological, social, and biological contributors to substance misuse [58].

These data underscore the need to develop a class of targeted interventions for people with mental health disorders who are at risk for opioid overdose. Broader reach and accessibility of mental health care locally in places hardest hit by the opioid epidemic could also assist in decreasing overdose rates by tackling the psychological symptoms that frequently add to misuse. The remaining non-prescription related strategies, better access to mental health care, stigma reduction, and social support for individuals with a mental illness, are all very reasonable and needed policies but are irrelevant against lessening opioid overdose [59].

Damage reduction, such as naloxone distribution and supervised consumption sites, should also be available to those who have mental health disorders that increase their risk of overdose. They stop people from dying today while we connect them with longer-term care. Merging services focusing on harm reduction and mental health matters would offer a complete method to decrease the associated overall harms while knowing these two are often interdependent.

**Future Research Directions**

Several limitations exist to this review despite the informative overview it provides. Additional research is needed to disentangle the specific pathways linking mental illness with opioid overdoses. In particular, studies tracking individuals over time (longitudinal) are required in order to further clarify whether or not symptomatology of mental health disorders pre-existed opioid use or if opioid use contributed negatively to the development of psychiatric symptoms [23]. These studies may also inform the search for moderators of this relationship (e.g., social support or access to healthcare) at different levels.

Future research should focus on the creation and examination of interventions designed to decrease opioid overdose risk for individuals with mental health disorders. Approaches to integrated care and harm reduction have potential for addressing the co-occurring challenges of mental health and substance use. To lower opioid overdose rates and treat individuals with co-morbid psychiatric illness and substance use disorders, these interventions mandate rigorous evaluation [18].

**Conclusion**

This review underscores the urgent imperative to integrate mental health disorders and substance use for both clinical care and public health response to opioid overdose. Prevalent evidence demonstrates that individuals with a variety of mental health disorders are at substantially increased risk for opioid overdose, although how this is occurring With the U.S. trends in mind, it is reported thatpeople might have to see this as newer material. With an integrated mental health and substance use care system, increased access to a wide range of mental health services, harm reduction strategies and more support systems in place we can start to unravel the tangled web created by such complex problems as mental health and opioid abuse. Additional research is needed to better elucidate these relationships and inform strategies for reducing the burden of opioid overdose among at-risk populations.

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