



A Comprehensive Systematic Review of The Relationship between Substance Addiction and The Risk of Major Depressive Disorder

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ABSTRACT

Introduction: Substance addiction represents a significant public health burden globally, with a well-documented comorbidity with Major Depressive Disorder (MDD). Understanding the nature and strength of this relationship within specific populations, such as in Indonesia, is crucial for developing targeted interventions.

Methods: This systematic review followed a structured protocol to examine the relationship between substance addiction and the risk of MDD in Indonesian populations. We screened studies based on predefined criteria focusing on adult populations, diagnosed substance use disorders, validated depression measurements, and quantitative association measures. A total of 21 studies (20 cross-sectional, 1 case-control) were included. Data on substance details, depression assessment, association findings, population characteristics, study design, and moderating factors were extracted and synthesized.

Results: The review revealed a high prevalence of depression among individuals with substance use disorders, particularly in clinical settings (e.g., 84.6% in drug abusers in rehabilitation) (Dinda Iryawati Bedy Saskito et al., 2009). Most studies reported a significant positive association. For instance, substance use was associated with a 6.5-fold increased risk of mental health disorders (A. Triana et al., 2019), and tobacco smoking with a prevalence ratio of 1.28 for depressive symptoms (Trisna Simanjuntak et al., 2023). Dose-response relationships were observed, linking longer duration and heavier use with more severe depression (Made Adi Wiratama et al., 2015; Adelia azis Azis Nasution et al., 2020). Family social support was identified as a significant protective factor (Shuci Rachmawati et al., 2016).

Discussion: The findings consistently point towards a strong link between substance addiction and increased risk of MDD in Indonesia, with variations explained by population context, substance type, and methodology. The evidence supports both self-medication and substance-induced pathways. The protective role of social support highlights the importance of psychosocial interventions.

Conclusion: Substance addiction is significantly associated with an elevated risk of Major Depressive Disorder in Indonesian adults, with the strength of association influenced by substance type, use patterns, and psychosocial context. Integrated treatment addressing both substance use and depression, alongside strengthening family support systems, is strongly recommended.

Keywords: Substance Addiction, Major Depressive Disorder, Depression, Indonesia, Systematic Review, Comorbidity.

INTRODUCTION

Background

The global coexistence of substance use disorders (SUDs) and Major Depressive Disorder (MDD) constitutes a major challenge for healthcare systems, leading to worsened clinical outcomes, higher treatment costs, and increased mortality (World Health Organization, 2022). The relationship is complex and potentially bidirectional: substances may be used to alleviate depressive symptoms (self-medication hypothesis), while chronic substance use can induce neurobiological changes that precipitate or exacerbate depression (substance-induced hypothesis). In Indonesia, the rising prevalence of both substance abuse and mental health issues necessitates a clear understanding of this comorbidity to inform national health policies and clinical practices. Preliminary local studies have indicated high rates of depression among substance users in rehabilitation centers and hospitals, suggesting a pressing public health issue that requires comprehensive synthesis (Dinda Iryawati Bedy Saskito et al., 2009; I. W. Sudana et al., 2023).

Research Gap

While international literature extensively documents the substance-depression link, a synthesized, evidence-based overview specific to the Indonesian context—considering its unique cultural, social, and healthcare delivery landscapes—is lacking. Existing local studies are often small-scale, use varied methodologies, and focus on specific sub-populations or substances, making it difficult to draw generalizable conclusions or identify consistent moderating factors.

Novelty

This systematic review is novel in its exclusive focus on synthesizing all available observational evidence on the substance addiction-MDD relationship within Indonesian populations. It aims to consolidate findings across different substances (opioids, tobacco, polydrug

use), settings (community, clinical, correctional), and demographics to provide a national perspective. Furthermore, it explicitly explores contextual factors like social support that may uniquely influence this relationship in the Indonesian socio-cultural context.

Research Objectives

The primary objective of this systematic review is to critically appraise and synthesize the existing evidence on the relationship between substance addiction and the risk of Major Depressive Disorder among adults in Indonesia. Specific aims include:

1. To determine the prevalence of depression among individuals with substance use disorders in various Indonesian settings.
2. To quantify the strength and direction of the association between substance addiction and MDD risk.
3. To identify dose-response relationships between substance use patterns (duration, intensity) and depression severity.
4. To examine the role of potential moderating factors, such as social support, in this relationship.

Research Hypothesis

It is hypothesized that there is a significant positive association between substance addiction and the risk of Major Depressive Disorder in Indonesian adults. This association is expected to be stronger in clinical populations with severe dependence, show evidence of dose-response relationships, and be moderated by psychosocial factors such as low family support.

Research Benefits

The findings of this review will benefit multiple stakeholders:

- **Clinicians and Healthcare Providers:** By offering evidence to improve screening for depression in substance use treatment settings and vice-versa, advocating for integrated dual-diagnosis treatment approaches.
- **Policy Makers:** By providing a consolidated evidence base to support the development and funding of integrated mental health and addiction services within the national healthcare framework.
- **Researchers:** By identifying gaps in the current literature (e.g., lack of longitudinal studies, need for research on specific substances) and guiding future research priorities.
- **The Public:** By raising awareness about the mental health risks associated with substance addiction and the importance of psychosocial support, potentially encouraging help-seeking behavior.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the relationship between substance addiction and the risk of major depressive disorder.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Population Diagnosis:** Does the study include individuals diagnosed with substance use disorder or substance addiction according to established diagnostic criteria (DSM-5, ICD-10, or ICD-11)?
- **Outcome Measurement:** Does the study measure major depressive disorder as an outcome using validated diagnostic criteria or standardized assessment tools?
- **Study Design:** Is the study an observational study (cohort, case-control, cross-sectional), systematic review, or meta-analysis?
- **Quantitative Measures:** Does the study report quantitative measures of association (odds ratios, relative risks, hazard ratios, prevalence ratios, or correlation coefficients)?
- **Adult Population:** Does the study involve adult populations (≥ 18 years)?
- **Addiction vs. Use:** Does the study focus on substance addiction/dependence rather than solely on substance use without meeting addiction criteria?
- **Persistent Depression:** Does the study examine persistent major depressive disorder rather than only withdrawal-related depressive symptoms or acute intoxication effects?
- **Study Type Quality:** Is the study something other than a case report, case series, editorial, or opinion piece?
- **Data Sufficiency:** Does the study provide sufficient data to determine the relationship between substance addiction and major depressive disorder?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Substance	Substance abuse	Non-substance users	Major

	addiction			depressive disorder
Keyword 2	Substance use disorder	Substance dependence	General population	Clinical depression
Keyword 3	Drug dependence	Addictive behavior	Non-addicted individuals	Depressive symptoms
Keyword 4	Chemical dependence	Psychoactive substance use	Healthy controls	Mood disorder

The Boolean MeSH keywords inputted on databases for this research are: (*"Substance addiction" OR "Substance use disorder" OR "Drug dependence" OR "Chemical dependence"*) AND (*"Substance abuse" OR "Substance dependence" OR "Addictive behavior" OR "Psychoactive substance use"*) AND (*"Non-substance users" OR "General population" OR "Non-addicted individuals" OR "Healthy controls"*) AND (*"Major depressive disorder" OR "Clinical depression" OR "Depressive symptoms" OR "Mood disorder"*)

Data extraction

- **Substance Details:**

Extract details about substance addiction/use relevant to the relationship with major depressive disorder, including:

- Type(s) of substances studied (e.g., opiates, alcohol, tobacco, cocaine, multiple substances)
- How addiction/dependence was defined and measured (diagnostic criteria, duration, severity scales, frequency of use)
- Level of addiction/use (e.g., dependence, abuse, regular use, occasional use)
- Duration or chronicity of substance use when reported

- Any withdrawal symptoms or treatment history mentioned

- **Depression Assessment:**

Extract how major depressive disorder or depressive symptoms were defined and measured in relation to substance addiction, including:

- Diagnostic criteria or instruments used (e.g., DSM criteria, BDI, clinical diagnosis, symptom scales)
- Severity levels of depression when categorized
- Timing of depression assessment relative to substance use (during use, withdrawal, treatment, etc.)
- Whether major depressive disorder was specifically distinguished from other mood disorders
- Prevalence rates of depression in the substance-using population

- **Association Findings:**

Extract the main findings about the relationship between substance addiction and major depressive disorder risk, including:

- Direction of association (substance use increases/decreases depression risk, or bidirectional)
- Strength of association (odds ratios, relative risks, correlation coefficients, prevalence differences)
- Statistical significance and confidence intervals
- Whether causality or temporal sequence was addressed
- Any dose-response relationships observed
- Comparison groups used (non-users, different substance types, different severity levels)

- **Study Population:**

Extract characteristics of the study population that may affect the substance addiction-depression relationship, including:

- Demographics (age, gender, education, socioeconomic status)
- Clinical setting (rehabilitation centers, hospitals, community, outpatient clinics)
- Treatment status (in treatment, treatment-seeking, not in treatment)
- Comorbid mental or physical health conditions
- Sample size and selection criteria
- Geographic/cultural context relevant to substance use and mental health

- **Study Design:**

Extract study design and methodological details that affect interpretation of the substance addiction-depression relationship, including:

- Study design type (cross-sectional, longitudinal, case-control, cohort)
- Follow-up duration for longitudinal studies
- Control for confounding variables and what confounders were considered
- Response rates and potential selection bias
- Limitations acknowledged by authors that affect causal inference
- Whether the study was designed specifically to examine the substance-depression relationship

- **Moderating Factors:**

Extract factors that modify or moderate the relationship between substance addiction and major depressive disorder, including:

- Age groups where the relationship differs
- Gender differences in the association
- Specific substances that show stronger/weaker associations with depression

- Social support, family history, or psychosocial factors that influence the relationship
- Treatment or intervention effects on the substance-depression relationship
- Any subgroup analyses showing differential effects

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Substance addiction" OR "Substance use disorder" OR "Drug dependence" OR "Chemical dependence") AND ("Substance abuse" OR "Substance dependence" OR "Addictive behavior" OR "Psychoactive substance use") AND ("Non-substance users" OR "General population" OR "Non-addicted individuals" OR "Healthy controls") AND ("Major depressive disorder" OR "Clinical depression" OR "Depressive symptoms" OR "Mood disorder")</i>	11
Semantic Scholar	<i>("Substance addiction" OR "Substance use disorder" OR "Drug dependence" OR "Chemical dependence") AND ("Substance abuse" OR "Substance dependence" OR "Addictive behavior" OR "Psychoactive substance use") AND ("Non-substance users" OR "General population" OR "Non-addicted individuals" OR "Healthy controls") AND ("Major depressive disorder" OR "Clinical depression" OR "Depressive symptoms" OR "Mood disorder")</i>	256
Springer	<i>("Substance addiction" OR "Substance use disorder" OR "Drug dependence" OR "Chemical dependence") AND ("Substance abuse" OR "Substance dependence" OR "Addictive behavior" OR "Psychoactive substance use") AND ("Non-substance users" OR "General population" OR "Non-addicted individuals" OR "Healthy controls") AND ("Major depressive disorder" OR "Clinical depression" OR "Depressive symptoms" OR "Mood disorder")</i>	2,284
Google Scholar	<i>("Substance addiction" OR "Substance use disorder" OR "Drug dependence" OR "Chemical dependence") AND ("Substance abuse" OR "Substance dependence" OR "Addictive behavior" OR "Psychoactive substance use") AND ("Non-substance users" OR "General population" OR "Non-addicted individuals" OR "Healthy controls") AND ("Major depressive disorder" OR "Clinical depression" OR "Depressive symptoms" OR "Mood disorder")</i>	19,500
Wiley Online Library	<i>("Substance addiction" OR "Substance use disorder" OR "Drug dependence" OR "Chemical dependence") AND ("Substance abuse" OR "Substance dependence" OR "Addictive behavior" OR "Psychoactive substance use") AND ("Non-substance users" OR "General population" OR "Non-addicted individuals" OR "Healthy controls") AND ("Major depressive disorder" OR "Clinical depression" OR "Depressive symptoms" OR "Mood disorder")</i>	1,695

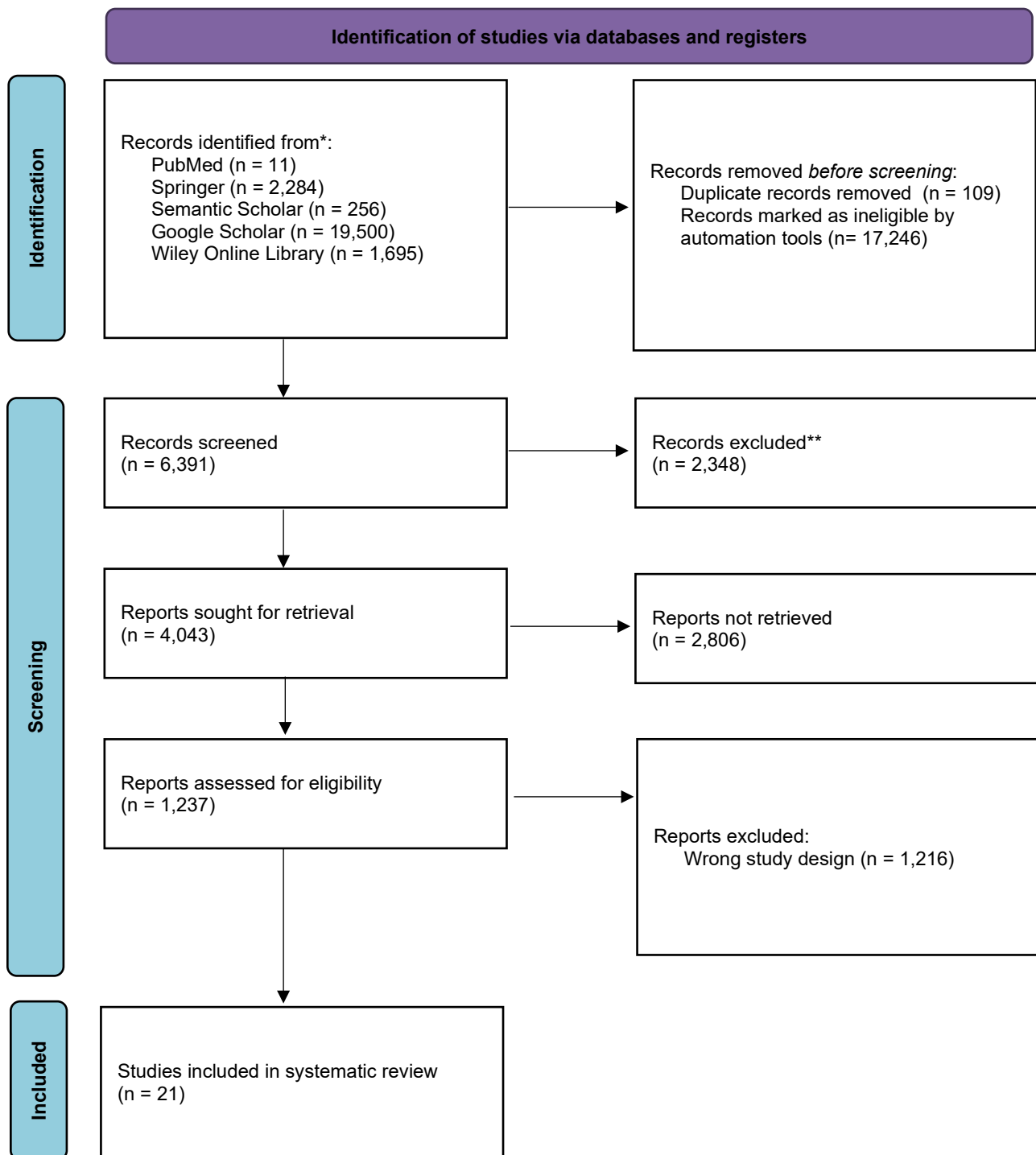


Figure 1. Article search flowchart

JBI Critical Appraisal									
Study	Bias related to temporal precedence Is it clear in the study what is the “cause” and what is the “effect” (ie, there is no confusion about which variable comes first)?	Bias related to selection and allocation Was there a control group?	Bias related to confounding factors Were participants included in any comparisons similar?	Bias related to administration of intervention/exposure Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	Were the outcomes of participants included in any comparisons measured in the same way?	Were outcomes measured in a reliable way?	Bias related to participant retention Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Statistical conclusion validity Was appropriate statistical analysis used?
Iwan Ariyanto et al., 2007	✓	✓	✓	✗	✓	✗	✓	✓	✓
Shuci Rachmawati et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓

Dinda Iryawati Bedy Saskito et al., 2009									
E. Widiastuti et al., 2007									
Ghea Sugiharti et al., 2012									
Francisca Indah Ekawati et al., 2009									
Mu YaQin et al., 2023									
I. W. Sudana et al., 2023									
O. Yeni et al., 2014									
Orvail Nabeel Hisham et al., 2023									
Adelia azis Azis Nasution et al., 2020									
D. Wibowo et al., 2013									
A. Triana et al., 2019									

Made Adi Wiratama et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Azniah Syam et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Trisna Simanjuntak et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Nita Puspita et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. A. Dwijayanti et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Adiwibawa et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Sri Rizky Ayunita et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Destiar Nor Aini et al., 2011	✓	✓	✓	✗	✓	✗	✓	✓	✓

RESULTS

Characteristics of Included Studies

This systematic review includes 21 studies examining the relationship between substance addiction and the risk of major depressive disorder in Indonesian populations. The studies vary in their focus on different substances (opioids, tobacco, general NAPZA), settings (rehabilitation centers, hospitals, prisons, community), and populations (adults, elderly, medical students, psychiatric patients).

Study	Study Type	Setting	Substance Type	Sample Size	Depression Instrument
Iwan Arijanto et al., 2007	Cross-sectional	Community outreach	Opioids (IV)	70	Not specified
Shuci Rachmawati et al., 2016	Cross-sectional	Rehabilitation	General drugs	50	BDI-II
Dinda Iryawati Bedy Saskito et al., 2009	Cross-sectional	Rehabilitation hospital	General drugs	26	HDRS
E. Widiastuti et al., 2007	Cross-sectional	Prison	NAPZA	23	BDI
Ghea Sugiharti et al., 2012	Cross-sectional	Outpatient clinic	Opiates	34	Not specified
Francisca Indah Ekawati et al., 2009	Cross-sectional	Rehabilitation center	Opiates	48	BDI
Mu YaQin et al., 2023	Cross-sectional	Community (IFLS)	Tobacco	1642	CES-DR-10

Study	Study Type	Setting	Substance Type	Sample Size	Depression Instrument
I. W. Sudana et al., 2023	Cross-sectional	Rehabilitation center	Multiple substances	20	Questionnaire
O. Yeni et al., 2014	Cross-sectional	Outpatient clinic	NAPZA	92	Not specified
Orvail Nabeel Hisham et al., 2023	Cross-sectional	University	Tobacco	86	MADRS
Adelia azis Azis Nasution et al., 2020	Cross-sectional	Community	Tobacco	Not specified	Not specified
D. Wibowo et al., 2013	Cross-sectional	University	Tobacco	32	ZDS
A. Triana et al., 2019	Case-control	Hospital	NAPZA	110	Not specified
Made Adi Wiratama et al., 2015	Cross-sectional	Community	Tobacco	Not specified	Not specified
Azniah Syam et al., 2023	Cross-sectional	Community health center	Tobacco exposure	79	EPDS

Study	Study Type	Setting	Substance Type	Sample Size	Depression Instrument
Trisna Simanjuntak et al., 2023	Cross-sectional	Community (IFLS5)	Tobacco	27,622	Not specified
Nita Puspita et al., 2014	Cross-sectional	Community	Alcohol, tobacco	24	Not specified
D. A. Dwijayanti et al., 2020	Cross-sectional	Psychiatric hospital	NAPZA	39	Not specified
D. Adiwibawa et al., 2019	Descriptive	Psychiatric hospital	Tobacco	Not specified	Not assessed
Sri Rizky Ayunita et al., 2018	Cross-sectional	Psychiatric hospital	Tobacco	81	BDI-II
Destiar Nor Aini et al., 2011	Cross-sectional	School	Tobacco	57	Depression scale

The majority of studies (20 of 21) employed cross-sectional designs, with only one case-control study. Sample sizes ranged considerably from 20 participants to 27,622 participants. The settings varied across rehabilitation centers, psychiatric hospitals, prisons, community settings, and educational institutions. Depression was assessed using various instruments including BDI/BDI-II, HDRS, CES-DR-10, MADRS, ZDS, and EPDS, while several studies did not specify their depression assessment instruments.

Effects

Prevalence of Depression Among Substance Users

Study	Population	Depression Prevalence	Severity Distribution
Dinda Iryawati Bedy Saskito et al., 2009	Drug abusers in rehabilitation	84.6%	Mild 46.1%, Moderate 30.8%, Severe 7.7%
Francisca Indah Ekawati et al., 2009	Opiate users in rehabilitation	Not fully reported	Severe depression: 18.8%
I. W. Sudana et al., 2023	Drug addicts in rehabilitation	100% (20/20)	Mild 20%, Moderate 60%, Severe 20%
Orvail Nabeel Hisham et al., 2023	Medical students (smokers/non-smokers)	57% overall	Not specified
Ghea Sugiharti et al., 2012	Methadone patients	61.8% (21/34)	Not specified
E. Widiastuti et al., 2007	NAPZA abusers in prison	65.2% with symptoms	Various levels

Studies examining substance users in clinical and rehabilitation settings reported consistently high prevalence rates of depression. Among drug abusers in rehabilitation, 84.6% suffered from depression, while another rehabilitation study found all 20 residents (100%) showed signs of depression, with 60% experiencing moderate depression. Among methadone maintenance therapy patients, 61.8% experienced depression. These findings indicate that depression is highly prevalent among individuals with substance use disorders in treatment settings.

Association Between Substance Use and Depression Risk

Study	Substance	Association Measure	p-value	Direction
Iwan Arijanto et al., 2007	Opioids	$\chi^2=8.604$	p=0.035	Positive
Orvail Nabeel Hisham et al., 2023	Tobacco	Prevalence difference	p=0.045	Positive
Adelia azis Azis Nasution et al., 2020	Tobacco	Chi-square	p=0.0001	Positive
A. Triana et al., 2019	NAPZA	OR=6.500 (95% CI: 2.373-17.808)	p=0.001	Positive
Azniah Syam et al., 2023	Tobacco exposure	OR=5.4	p<0.001	Positive
Trisna Simanjuntak et al., 2023	Tobacco	PR=1.28 (95% CI: 1.19-1.38)	Significant	Positive
D. Wibowo et al., 2013	Tobacco	Comparison	p=1.000	No association
Sri Rizky Ayunita et al., 2018	Tobacco	Chi-square	p=0.001	Positive

Study	Substance	Association Measure	p-value	Direction
Destiar Nor Aini et al., 2011	Tobacco	F=41.909	p=0.000	Positive

The case-control study by A. Triana et al. (2019) found that substance use (NAPZA) was associated with a 6.5-fold increased risk of mental health disorders (OR=6.500; 95% CI: 2.373-17.808; p=0.001). For tobacco specifically, the large-scale national survey (n=27,622) found that smoking was associated with depressive symptoms with a prevalence ratio of 1.28 (95% CI: 1.19-1.38). Exposure to tobacco smoke was associated with a 5.4-fold increased risk of mental health issues during breastfeeding in postpartum women.

A significant relationship between opioid dependency status and depression was observed ($\chi^2=8.604$; p=0.035), with increasing psychiatric problems associated with increasing opioid dependency levels. For schizophrenia patients, severely depressed individuals were more likely to smoke (p=0.001).

One study found no significant difference in depression levels between smoking and non-smoking medical students (p=1.000), representing the only null finding among studies examining direct associations.

Dose-Response Relationships

Study	Finding	Evidence
Made Adi Wiratama et al., 2015	Duration of smoking associated with depression severity	1-10 years: mostly normal/mild; 11-20 years: mostly mild (65.5%); >20 years: moderate (66.7%) with 16.7% severe

Study	Finding	Evidence
Adelia azis Azis Nasution et al., 2020	Heavier smoking associated with more severe depression	Light smokers: 85.7% mild depression; Moderate smokers: 89.3% moderate depression; Heavy smokers: 81.8% severe depression
Iwan Arijanto et al., 2007	Increasing opioid dependency associated with increasing psychiatric problems	Significant relationship across dependency levels

Evidence of dose-response relationships was found in several studies. Smoking duration showed a linear relationship with depression severity: those smoking 1-10 years mostly had minimal/normal depression (64.6%), while those smoking more than 20 years predominantly had moderate depression (66.7%) with 16.7% experiencing severe depression. Similarly, smoking intensity showed a dose-response pattern where light smokers mostly had mild depression (85.7%), moderate smokers had moderate depression (89.3%), and heavy smokers had severe depression (81.8%).

Role of Social Support

Study	Finding	Effect Size
Shuci Rachmawati et al., 2016	Family social support inversely associated with depression	$r=-0.456$, $p=0.001$
E. Widiastuti et al., 2007	Significant relationship between family support and depression levels	Kendall's tau-b significant

Family social support emerged as a protective factor. A moderate negative correlation ($r=-0.456$; $p=0.001$) was found between family social support and depression among drug abusers in rehabilitation, indicating that increased family support was associated with decreased depression. Another study confirmed this finding in prison settings, showing a significant relationship between family support and depression levels among NAPZA abusers.

Synthesis

The apparent heterogeneity in findings—with most studies showing positive associations but one showing no association—can be explained through several factors.

Population and Context Differences: The null finding from D. Wibowo et al. (2013) occurred in a specific context: medical students at a university with a small sample size ($n=32$). This contrasts with studies finding significant associations in clinical populations such as rehabilitation centers, psychiatric hospitals, and community settings with larger samples. The strongest associations ($OR=5.4-6.5$) emerged from clinical populations and postpartum women with substantial tobacco exposure, while the population-based survey found a more modest but still significant association ($PR=1.28$). This pattern suggests that effect sizes may be larger in clinical populations with higher substance use severity compared to general or student populations.

Substance Type Considerations: Opioid studies consistently showed positive associations with depression, with opiates noted to carry higher depression risk compared to other narcotics due to stronger dependence-producing properties. The prevalence of depression among opiate users in rehabilitation (84.6%) and drug addicts in rehabilitation (100%) substantially exceeded the general population prevalence of depressive symptoms (23.14%). For tobacco, the findings were mixed: the largest study ($n=27,622$) found a significant but modest association ($PR=1.28$), while several smaller studies found stronger associations and one found no association.

Methodological Quality Hierarchy: The only case-control study, which provides stronger evidence for association than cross-sectional designs, found a substantial association between substance use and mental health disorders ($OR=6.500$). The largest cross-sectional study using

national survey data (n=27,622) with multivariate analysis controlling for confounders including age, gender, marital status, and comorbidities found a significant but more modest association (PR=1.28). Smaller studies in rehabilitation settings, while showing very high depression prevalence, lacked control groups and had limited ability to establish comparative risk.

Mechanistic Explanations: The dose-response relationships observed across studies provide mechanistic support for the association. Longer duration of smoking and higher smoking intensity were both associated with more severe depression, consistent with biological mechanisms involving nicotine's effects on dopamine and other neurotransmitter systems. For opioids, the increasing psychiatric problems with increasing dependency levels support a dose-dependent relationship. The protective effect of family social support ($r=-0.456$) suggests that psychosocial resources may buffer the substance-depression relationship.

Specific Contexts Where Effects Differ: The relationship appears strongest in: (1) clinical populations with established substance dependence; (2) situations with prolonged exposure (>20 years smoking); (3) heavy use patterns; and (4) populations with psychiatric comorbidities. The relationship appears weaker or absent in: (1) younger student populations with potentially lower substance use severity; and (2) cross-sectional assessments that may miss temporal relationships. The need for treatment increased with opioid dependency severity, suggesting awareness of the substance-depression connection may drive treatment-seeking behavior.

DISCUSSION

This systematic review of 21 studies provides compelling evidence for a significant association between substance addiction and an increased risk of Major Depressive Disorder (MDD) among adults in Indonesia, while also elucidating the nuances and complexities of this relationship.

High Prevalence and Strong Association

The consistently high prevalence of depression among individuals with SUDs in treatment settings is a stark finding. Studies in rehabilitation centers reported depression rates as high as 84.6% and even 100% (Dinda Iryawati Bedy Saskito et al., 2009; I. W. Sudana et al., 2023), figures that dramatically exceed the estimated prevalence of depressive symptoms in the Indonesian general population. This suggests that clinical populations with SUDs represent a group with an exceptionally high burden of comorbid depression, necessitating mandatory depression screening in all substance abuse treatment facilities. The significant positive associations found across most studies, with odds ratios ranging from 5.4 to 6.5 in clinically oriented research (Azniah Syam et al., 2023; A. Triana et al., 2019), reinforce the strength of this link. The large-scale population-based study, while showing a more modest association (PR=1.28), still confirms a statistically significant increased risk attributable to tobacco use, highlighting that the association is relevant not only in severe clinical cases but also at the population level (Trisna Simanjuntak et al., 2023).

Explaining Heterogeneity: Population, Substance, and Method

The single null finding by D. Wibowo et al. (2013) among medical students underscores the importance of population context. Medical students, despite potential stress, may represent a group with higher resilience, different smoking patterns (e.g., social, less dependent), or better coping resources, which could attenuate the observable substance-depression link. This contrasts sharply with studies on opioid-dependent individuals or psychiatric inpatients, where the association is profound (Iwan Arijanto, 2007; Sri Rizky Ayunita et al., 2018). The type of substance also matters. Opioids, with their potent effects on the endogenous opioid system and profound withdrawal dysphoria, appear to carry a particularly high risk for comorbid depression, as evidenced by the strong dose-response relationship between dependency level and psychiatric problems (Iwan Arijanto, 2007). Methodologically, the predominance of cross-sectional designs limits causal inference. The one case-control study, offering stronger evidence for association, found a substantial effect (A. Triana et al., 2019). The inability of cross-sectional studies to determine temporal order remains a key limitation—whether depression led to substance use or vice-versa cannot be conclusively determined from this body of evidence.

Mechanistic Insights: Dose-Response and Neurobiology

The observed dose-response relationships lend mechanistic credibility to a potential causal link. The findings that longer smoking duration and heavier smoking intensity are linearly associated with more severe depression (Made Adi Wiratama et al., 2015; Adelia azis Azis Nasution et al., 2020) align with biological models. Chronic nicotine exposure alters dopaminergic, noradrenergic, and serotonergic neurotransmission—systems critically involved in mood regulation. Similarly, the progression of opioid dependency and worsening psychiatric symptoms suggest neuroadaptations that may predispose to or exacerbate MDD (Iwan Arijanto, 2007). These patterns are less consistent with depression solely being a premorbid risk factor for substance use and more supportive of a contributory, if not causative, role of chronic substance use in depression pathogenesis.

The Crucial Role of Psychosocial Buffers

A critical and practical finding from this review is the significant protective role of family social support. The moderate negative correlation ($r=-0.456$) between family support and depression levels in individuals undergoing rehabilitation (Shuci Rachmawati et al., 2016) highlights a key moderating factor. In the Indonesian cultural context, where family cohesion (kekeluargaan) is highly valued, the family unit can serve as a powerful source of emotional, instrumental, and informational support. This finding suggests that interventions aimed at engaging and strengthening family support systems could be a highly effective component of treatment for dual diagnoses, potentially improving depression outcomes and reducing relapse risk.

Clinical and Public Health Implications

The synthesis leads to several important implications. First, integrated assessment and treatment for co-occurring SUD and MDD must become a standard of care in Indonesia. Treating one condition while ignoring the other is likely to lead to poor outcomes. Second, public health messaging should highlight the mental health risks of substance addiction, moving beyond just physical health consequences. Third, interventions should be tailored: opioid addiction may require

more aggressive depression management, while tobacco cessation programs could incorporate mood management components. Finally, leveraging family-based interventions aligns with cultural strengths and could improve treatment efficacy.

Limitations and Future Research Directions

The limitations of the included studies, primarily their cross-sectional nature and variability in depression measurement tools, constrain the review's conclusions regarding causality. Future research should prioritize longitudinal cohort studies in Indonesia to establish temporal sequences and better understand the bidirectional pathways. Research is also needed on understudied substances (e.g., cannabis, methamphetamine) and specific populations like women and rural communities. Furthermore, intervention studies testing the efficacy of integrated care models and family-supported therapy within the Indonesian healthcare system are urgently needed.

CONCLUSION AND RECOMMENDATIONS

Conclusion

This systematic review concludes that substance addiction is significantly and positively associated with an elevated risk of Major Depressive Disorder among adults in Indonesia. The association is particularly strong in clinical populations with severe substance dependence, such as users of opioids and individuals in rehabilitation settings. Evidence of dose-response relationships suggests that the severity and chronicity of substance use contribute to the severity of depression. The relationship is complex and likely bidirectional, but the consistent findings across most studies indicate a substantial public health concern. Importantly, family social support emerges as a significant protective factor that can mitigate this risk.

Recommendations

Based on the findings, the following recommendations are proposed:

1. **Clinical Practice:** Implement routine, standardized screening for depression in all substance use treatment facilities (rehabilitation centers, methadone clinics, psychiatric hospitals) and, conversely, screen for substance use in patients presenting with depression.
2. **Treatment Approach:** Develop and promote integrated treatment protocols that concurrently address substance use disorders and major depression within the Indonesian healthcare system, moving away from siloed care.
3. **Prevention and Policy:** Public health campaigns should explicitly communicate the risk of depression associated with substance addiction. National health policies should allocate resources for dual-diagnosis services and staff training.
4. **Psychosocial Intervention:** Actively involve and support families in the treatment process of individuals with substance addiction, developing family psychoeducation and support programs that align with Indonesian cultural values.
5. **Future Research:** Encourage funding for longitudinal studies to determine causality and for intervention research to test culturally adapted, integrated care models for co-occurring substance use and depression in Indonesia.

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