

Drug-Related Problems and Associated Factors in Depressive Disorders: A Systematic Review

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Abstract. *Depressive disorders are mental health condition marked by a persistent moody mood or loss of pleasure or interest in activities. It is commonly associated with complex treatment regimens and multiple coexisting conditions, which can lead to drug-related problems compromising treatment outcome. This systematic review aimed to identify the types of drug-related problems and factors associated among patients with depressive disorders. The review was conducted following the PRISMA 2020 guidelines, and a comprehensive literature search was conducted in PubMed and Scopus studies published between 2015-2025. The most frequently reported drug-related problems were polypharmacy, drug interactions, adverse drug reactions, medication non adherence, inappropriate prescribing, and undertreatment. Factor associated with the occurrence of drug-related problems included female sex, low educational level, unemployment, disease severity, psychiatric comorbidities, polypharmacy, prolonged treatment duration, limited access to healthcare services, and socioeconomic constraints. Polypharmacy was the most consistently reported factor across studies. In conclusion, drug-related problems are common among patients with depressive disorders and are influenced by multiple patient disease, medication, and healthcare-related factors. Regular medication review and monitoring are essential to improve medication safety and optimize treatment outcomes.*

Keywords: *Depressive Disorders, Drug-Related Problems, Risk Factors*

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INTRODUCTION

Depressive disorders are a common mental disorder. This condition is defined by persistent low mood or a diminished enjoyment or interest in activities for an extended duration (Rakofsky & Rapaport, 2018; Sharan & Vellapandian, 2024). Depression affects more than 280 million individuals globally and is acknowledged as a significant factor in Disability-Adjusted Life Years (DALYs) (Liu et al., 2024; Chen et al., 2026; Yang et al., 2025). Depression is prevalent globally, impacting millions of individuals across continents and across all age groups. Therefore, depression is not only a challenge for individuals, but also for society (Agustin et al., 2025). A survey of 5,725 adults reported that 14.1% experienced depressive symptoms based on the PHQ-4 screening instrument.

According to Sagar et al. (2017) and Evans-Lacko & Knapp (2016) Although depression has a fairly high prevalence, almost all individuals who show symptoms of depression have never received an official diagnosis from health workers. These findings indicate that there are still many cases of depression that have not been detected or have not received adequate treatment (McIntyre et al., 2023; Moitra et al., 2022). Therefore, the existence of this condition has the potential to increase the burden of disease, reduce the quality of life, and disrupt individual social function and productivity if not treated optimally (Chodavadia et al., 2023; Demain et al., 2015; Dreno et al., 2021; Buttery et al., 2021).

Management of depression does not only focus on the use of antidepressants, but also often involves the management of various comorbid conditions that accompany the patient (Gold et al., 2020; Thom et al., 2019; Malhi et al., 2018; Solmi et al., 2020). Various studies show that anxiety disorders, sleep disorders, cardiovascular diseases, and metabolic disorders are common comorbidities found in depressed patients (Wiersema et al., 2022). Consequently these patients often require multiple medications simultaneously, increasing the likelihood of polypharmacy (Ghaed-Sharaf et al., 2022; Muth et al., 2019). The existence of these comorbidities causes the use of several drugs at the same time (polypharmacy) to be difficult to avoid. Although often necessary, polypharmacy can heighten the risk of complications related to medications and affect the safety of treatment (Latas et al., 2024). Therefore, assessing medication usage in individuals with depressive disorders is crucial to guarantee the safety and efficacy of the prescribed therapies.

Drug-related problems are situations or events linked to medication therapy that actually or potentially interfere with achieving intended health outcomes, either currently or in the future. These issues encompass treatment efficacy, safety, and other outcomes related to therapy. Individuals with depressive disorders are particularly at risk for different types of DRPs due to the presence of numerous additional health conditions and the common practice of using multiple medications at the same time. Previous research indicates that adverse reactions to drug and interaction between them are among the most frequently reported drug-related problems for this demographic (Mateti et al., 2015; Angamo et al., 2016; Yadesa et al., 2021; Cahir et al., 2023). Factors such as age, the number of medications used, and comorbidities have been linked to an elevated risk of DRPs.

Despite various systematic reviews have evaluated DRPs in chronic diseases such as diabetes and cardiovascular disorders, no comprehensive review has specifically synthesized the spectrum of DRPs and associated factors among patients with depressive disorders. Consequently, this systematic review was performed to gather and synthesize existing evidence concerning drug-related problems and factors associated with their occurrence in patients diagnosed with depressive disorders. The findings of this review are expected to provide evidence-based information for healthcare professionals in identifying high risk patients and developing strategies to improve medication safety and optimize therapeutic outcomes.

METHODS

Study Design

This study was carried out as a systematic review in accordance with the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) 2020 guidelines. The objective of this systematic review was conducted to identify Drug-Related Problems (DRPs) and associated factors in individuals suffering depression. Included studies were observational studies that included patients diagnosed with depressive disorders.

Eligibility Criteria

This review encompassed observational studies (cross-sectional, cohort, and case-control studies) involving patients diagnosed with depressive disorders according to established diagnostic criteria. Drug-related problems included, but were not limited to medication-related problems, adverse drug reactions, drug interactions, inappropriate prescribing, polypharmacy, or other medication-related issues among patients with depressive disorders. Studies were excluded if they were reviews, editorial meta-analyses, letters to editors, and case reports, studies that did not involve patients with depressive disorders, did not report DRPs or associated factors, and articles without full-text access or duplicate publications.

Data Sources and Search Strategy

Literature searches were performed on PubMed and Scopus for studies published from January 2015 to December 2025. The approach utilized a combination of keywords related to

depressive disorders and drug-related problems using Boolean operators. Keywords used in pubmed and scopus were (“Depressive Disorder”[Mesh] OR depression [tiab] OR “depressive disorder*”[tiab] OR “major depressive disorder*”[tiab]) AND (“drug-related problem*”[tiab] OR “drug related problem*”[tiab] OR “medication-related problem*”[tiab] OR “medication related problem*”[tiab] OR “treatment-related problem*”[tiab]). The search strategy was adapted for each database.

Quality Assessment

The quality of the methodological research was evaluated with the Joanna Briggs Institute (JBI) critical appraisal tools in accordance with the research design (Table 1). Disagreements were resolved through discussion until an agreement was reached.

Table 1. Study Quality Assessment Results

Author, Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Score	Quality
(Brisnik et al., 2025)	V	V	V	V	V	V	V	V	-	-	-	8/8	High
(Chanie et al., 2025)	V	V	V	V	V	V	V	V	-	-	-	8/8	High
(Chen & Ding, 2023)	V	V	V	V	V	V	V	V	-	-	-	8/8	High
(Marasine et al., 2020)	V	V	V	V	V	V	V	V	-	-	-	8/8	High
(Abegaz et al., 2017)	V	V	V	V	V	V	V	-	-	-	-	7/8	High
(Sankhi et al., 2020)	V	V	V	V	X	X	V	V	V	X	X	8/11	Moderate
(Laux et al., 2017)	V	V	V	V	V	V	V	V	V	X	V	10/11	High
(Morze et al., 2024)	V	V	V	V	V	V	V	V	X	V	V	10/11	High
(Gomes et al., 2017)	V	V	V	X	X	V	V	V	V	X	X	8/11	Moderate
(Hoshtynar et al., 2025)	V	V	V	V	V	V	V	V	-	-	-	8/8	High
(Görnert et al., 2026)	V	V	V	V	V	V	V	V	V	V	V	11/11	High

Data Synthesis

A narrative synthesis was executed to summarize the different types of DRPs and their associated factors identified across studies. Considering the differences in the definitions of DRPs across studies, drug-related problems were extracted as described by the original authors. A meta-analysis was not conducted due to expected variation in study designs, definitions of outcomes, and reported predictors.

Study Selection

All gathered records were uploaded into reference management software, and duplicates were identified and eliminated. The selected articles underwent a two-step process that included screening the titles and abstracts, followed by a full-text evaluation based on set inclusion and

exclusion criteria. The selection process was recorded using a PRISMA 2020 flow diagram (Figure 1).

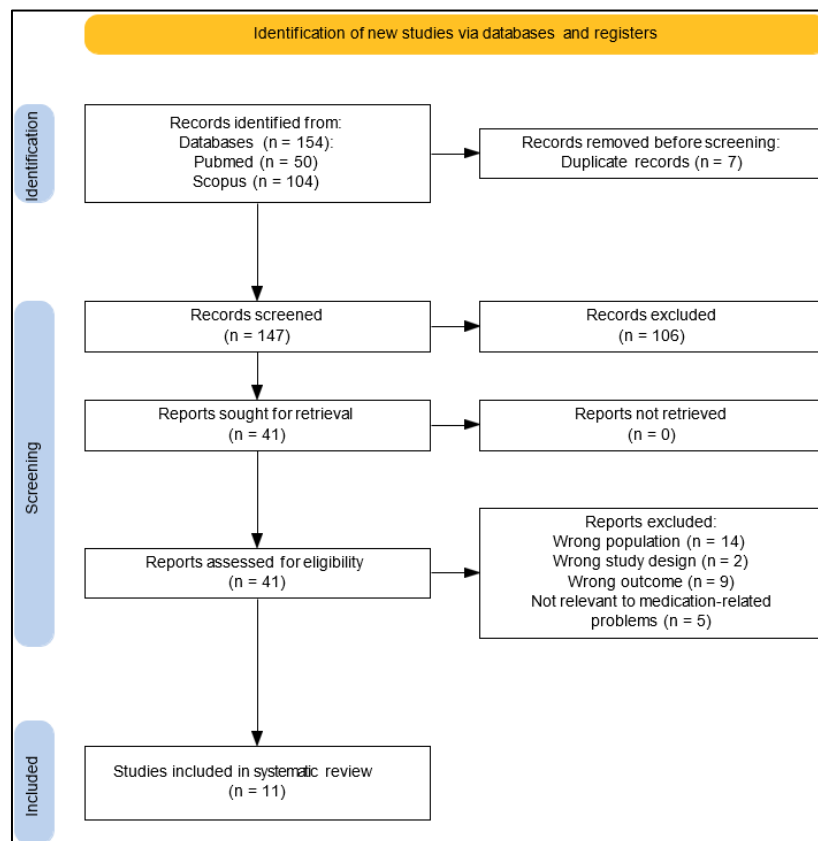


Figure 1. PRISMA Flow Diagram

RESULT AND DISCUSSION

A systematic review identified several types of Drug-Related Problems (DRPs) in patients suffering from depressive disorders, including polypharmacy, interaction between drugs, adverse drug reactions (ADRs), inappropriate prescribing, undertreatment, and medication non adherence. These findings indicate that patients with depression are particularly vulnerable to DRPs because treatment often involves long-term pharmacotherapy and management of multiple psychiatric and physical comorbidities. DRPs refer to incidents or situations related to drug treatment that may actual or potential to disrupt expected health results.

Drug-Related Issues Found

According to the findings from a systematic review, the most frequently observed drug-related problems (DRPs) found in patients diagnosed depressive disorder include ADRs, DDIs, and inappropriate prescribing (Table 2). Several studies indicate that ADRs and non adherence are the most common DRPs. A study found that 85.7% of participants experienced an adverse drug reaction and had low medication adherence at a rate of 57.1% (Abegaz et al., 2017). The results align with the conclusion of a systematic review, which determined that side effects from antidepressants lead to increased instances of medication non adherence in patients with depression. Side effects such as somnolence, headaches, gastrointestinal disturbances, and weight gain can reduce patient comfort, increasing the risk of premature discontinuation of therapy (Niarchou et al., 2024; Pannu & Goyal, 2025; Fluyau et al., 2018; Santarsieri & Schwartz, 2015).

Futhermore, polypharmacy and potential drug interaction are also frequently reported DRPs. A retrospective study in Ukraine found polypharmacy in 84% of patients and clinically significant DDIs in 42% (Hoshtynar et al., 2025). This finding is in line with studies who reported

that polypharmacy is a significant contributor to adverse drug reactions and interactions between medication, particularly among patients receiving multiple long-term medications (Alomar, 2014; Sommer et al., 2020). Furthermore, WHO identified polypharmacy as one of the main contributors to drug-related problems and emphasizes medication review as an important strategy to improve medication safety.

The overall result of this systematic review suggest that DRPs in patients with depressive disorders are dominated by ADRs, medication adherence, polypharmacy, and drug interactions. The emergence of these various DRPs is likely due to the high complexity of therapy, long-term medication use, and the presence of comorbidities requiring additional therapy. This situation indicates that patients with depressive disorders are a group that requires ongoing therapy monitoring to minimize the risk of medication-related harm and optimize treatment outcomes.

Table 2. Characteristics of Included Studies and Reported Drug-Related Problems Among Patients with Depressive Disorders

Author (Year)	Country	Study Design	Population/ Sample Size	DRPs Identified	Associated Factors
(Hoshtynar et al., 2025)	Ukraine	Retrospective analysis	Hospitalized patients with anxiety-depressive disorders (n=55)	Polypharmacy (84%), clinically significant DDIs (42%), and contraindicated prescribing (29%)	Age (correlated with number of drugs and comorbid conditions), polypharmacy, number of comorbid conditions
(Brisnik et al., 2025)	Germany	Cross-sectional analysis	Inpatient and outpatients with symptoms of depression (n=1671)	A significant treatment response inadequacy (80.1%), high-risk prescribing (21.7%), and potential insufficient treatment (42.1% of severe cases)	Polypharmacy (risk for high risk use), higher anxiety levels (risk for inadequate response), and higher education
(Gomes et al., 2017)	Brazil	Follow-up study	Patients with depression (n=20)	DRPs requiring pharmaceutical intervention, including non adherence and adverse effects	Poverty, family ruptures, history of violence, and comorbid physical illnesses
(Morze et al., 2024)	Poland	Prospective observational study	Breastfeeding with depressive spectrum disorders (n=47)	An insufficient treatment effect arises from either lower dose or medication non adherence (57.1%), adverse events in infants (8.5% linked to maternal medication)	Maternal concern regarding medication safety, breastfeeding goals, and polytherapy

(Chen & Ding, 2023)	China	Cross-sectional retrospective study	Outpatients with depression (n=6445)	Potential drug-drug interaction in 31% of prescriptions	Number of concomitant drugs (OR 7.86 for ≥ 7 drugs), principal diagnosis recurrent depressive disorder OR 1.18), and severity of disease
(Laux et al., 2017)	Germany	Pooled analysis of four prospective, non interventional studies	Outpatients with MDD (9601)	Adverse drug reactions reported for 5.32% of patients	Female gender (trend for transaminase elevations), psychotropic co medication, and initial phase of treatment (first 12 weeks)
(Chanie et al., 2025)	Ethiopia	Multicenter cross-sectional study	Patients with major depressive disorder at psychiatric clinics in public hospitals (n=422)	Non adherence to antidepressant medication (32.9%), severe adverse drug reactions (26.5%)	Female gender (AOR 3.29), illiteracy (AOR 2.17), unemployment (AOR 3.40), treatment duration > 25 months (AOR 1.89), and severe ADRs (AOR 3.94)
(Abegaz et al., 2017)	Ethiopia	Prospective hospital based cross-sectional study	Depression patients (n=217)	Low medication adherence (57.1%), ADR prevalence (85.7%), most common ADR was weight gain (13.2%)	Long duration of disease (AOR 2.42), long distance from hospital (AOR 5.06), and concomitant psychiatric illness (AOR 2.22)
(Marasine et al., 2020)	Nepal	Prospective cross-sectional study	Depression patients (n=174)	Adverse effects (74.13%), low medication adherence (52.29%)	Female gender (AOR 1.001), illiteracy (AOR 1.342), unemployment (AOR 1.46), and severity of ADRs
(Sankhi et al., 2020)	Nepal	Hospital based prospective observational study	Depression patients (n=47)	Adverse drug reactions (incidence 4.54%)	Female gender (higher incidence of 5.56%), age group 31-40 years, pharmacokinetic, hormonal, and immunological differences

(Görnert et al., 2026)	Germany	Clinical cohort study	Hospitalized patients with MDD	ADRR (average 5.9 per patient)	Polypharmacy (48.57% phenoconversion rate), combined non-normal CYP2C19/CYP2D6 metabolic status (p=0.039), higher age, and male sex
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Factors Associated with the Occurrence of DRPs

This systematic review identified various factors linked to the development of DRPs in individuals suffering from depressive disorders (Table 3). The analysis categorized these elements into several groups: sociodemographic factors, disease-related factors, disease-related factors, treatment-related factors, health-related factors, and socio-economic factors. The most frequently reported sociodemographic factors included female gender, low education level, and unemployment. Patients with low levels of education, limited social support, and limited economic conditions tend to have a higher risk of medication non-adherence and suboptimal therapy outcomes. The results are consistent with qualitative studies showing that patient-related factors, such as medication beliefs, perceived side effects, and support from family and healthcare professionals influence adherence to antidepressant use (Ho et al., 2017). Furthermore, patients with major depression or psychiatric comorbidities require more complex therapy, potentially increasing the risk of developing DRPs. This is consistent with guidelines that indicate those with more complicated conditions often necessitate more intensive treatment, thereby increasing the chances of experiencing drug-related problems.

Medication-related factors are the most commonly recognized contributors to DRPs. Engaging in multiple medication (polypharmacy), combinations of psychotropic medications, and long-term therapy can elevate the chances of experiencing adverse drug reactions, drug interactions, and lack of adherence. These align with studies found that ADRs are a major cause of changes in therapy regimens and treatment discontinuation in patients with major depressive disorder. Therefore, regular therapy monitoring, identification of potential drug interactions, and patient education regarding proper drug use are necessary to minimize the occurrence of DRPs and increase the success of therapy in patients with depressive disorders. In addition to medication-related factors, health care and socioeconomic factors such as limited access to health facilities, long distance to the hospital, poverty, and lack of social support have been identified as linked to the presence of drug-related problems (DRPs). These results indicate that the emergence of DRPs in patients with depressive disorder is influenced not only by disease characteristics and treatment, but also by social conditions and the health care system that supports the patient's treatment process (Parmar et al., 2023).

Table 3. Factors Associated with Drug-Related Problems (DRPs) Problems Among Patients with Depressive Disorders

Factor Group	Specific Factors	Impact on DRPs	Support Studies
Sociodemographic factors	Female sex, low educational level (illiteracy), unemployment	Increased incidence of ADRs and significantly higher medication non-adherence	(Abegaz et al., 2017; Chanie et al., 2025; Laux et al., 2017; Marasine et al., 2020)
Disease-related factors	Disease severity, recurrent depression (F33), psychiatric comorbidities	Increased occurrence of DRPs, potential for drug-drug interactions, and poor clinical outcomes or inadequate response	(Abegaz et al., 2017; Brisnik et al., 2025; Chen & Ding, 2023)

Medication-related factors	Polypharmacy (5 drugs), psychotropic medication, prolonged treatment duration (>25 month), genetic phenotypes (CYP2C19/CYP2D6)	Increased risks of DDIs, higher number of ADRs, and inappropriate (high risk) prescribing	(Chen & Ding, 2023; Görnert et al., 2026; Hoshtynar et al., 2025; Laux et al., 2017)
Healthcare-related factors	Limited access to specialized care. Long distance from the hospital (2 hours)	Reduced medication adherence due to difficulties in routine follow up and prescription refills	(Abegaz et al., 2017)
Socioeconomic factors	Poverty, financial constraints, family stressors, lack of social support	Increased non adherence and other treatment-related DRPs, reduce patient resilience	(Chanie et al., 2025; Gomes et al., 2017)

Clinical Implications

This conclusions from this review underscore the significant contribution of clinical pharmacist in identifying and preventing DRPs among patients with depressive disorders. Regular medication review, assessment of potential DDIs, monitoring of ADRs, and patient counseling may help reduce medication-related risks. Particularly attention should be directed toward patientes with polypharmacy, severe depression, psychiatric comorbidities, and socioeconomic vulnerabilities, as these groups appear to be at the highest risk of DRPs.

Strengths and Limitation

This review synthesized evidence from multiple countries and healthcare setting, providing a comprehensive overview of DRPs among patients with depressive disorders. However, heterogeneity in study design, DRP definition, and outcome measurements limited direct comparisons across studies. In addition, most included studies were observational, which may restrict causal interpretation of identified associated factors.

CONCLUSION

This systematic review found that the most commonly reported drug-related problems among patients dealing with depressive disorders included adverse drug reactions, medication non-adherence, polypharmacy, and drug-drug interactions were the most frequently reported drug-related problems among patients with depressive disorders. The presence of these issues was linked to various sociodemographic, disease-related, medication-related, healthcare-related, and socioeconomic factors, with polypharmacy emerging as the most consistently reported factor.

SUGGESTION

These insight emphasize the necessity for careful medication evaluation and oversight to improve medication safety and optimize treatment outcomes in patients with depressive disorders.

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