JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Review

The overlooked burden: anxiety and depression in patients with tuberculosis

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Abstract

Background: Tuberculosis (TB) is a major global cause of infectious disease–related morbidity and mortality. Beyond its physical burden, TB is associated with significant psychological distress. Anxiety and depression are highly prevalent among TB patients but often remain underrecognized and undertreated, despite their negative impact on treatment adherence, disease outcomes, and quality of life.

Objective: This review summarizes current evidence on the prevalence, biological mechanisms, treatment-related factors, and psychosocial determinants of anxiety and depression in patients with TB, and highlights the importance of routine mental health screening in integrated TB care.

Methodology: A narrative review of the literature was conducted focusing on epidemiology, underlying biological pathways, neuropsychiatric effects of anti-tuberculosis medications, psychosocial risk factors, and validated screening tools for anxiety and depression in TB populations.

Results: Depression affects nearly 45% of TB patients, while anxiety is present in 32–38%, with higher prevalence in low- and middle-income countries and among patients with multidrug-resistant TB. Biological mechanisms include chronic inflammation, cytokine-mediated neuroinflammation, hypothalamic–pituitary–adrenal axis dysregulation, altered tryptophan metabolism, and neuropsychiatric effects of medications such as isoniazid and cycloserine. Psychosocial factors, including stigma, social isolation, poverty, and limited social support, further contribute to psychological distress. Screening tools such as PHQ-9, GAD-7, HADS, and Zung SAS have demonstrated feasibility and validity in TB settings.

Conclusions: Anxiety and depression in TB result from interacting biological, pharmacological, and psychosocial factors. Integrating systematic and repeated mental health screening into routine TB care is essential to improve detection, support timely interventions, enhance adherence, and optimize treatment outcomes.

Key words: anxiety; depression; tuberculosis.

J Infect Dev Ctries 2026; 20(6):772-779. doi:10.3855/jidc.22967

(Received 25 January 2026 – Accepted 18 February 2026)

Introduction

Tuberculosis (TB) remains a major global health challenge, ranking among the top infectious disease killers worldwide. According to the World Health Organization, approximately 10.6 million people fell ill with TB in 2022, and 1.3 million died from the disease, underscoring its persistent burden despite decades of public health interventions [1,2]. Tuberculosis represents a prototypical syndemic disease, as its transmission, clinical course, and outcomes are shaped by the synergistic interaction between biological factors, comorbid conditions (such as HIV infection and diabetes mellitus), and adverse social determinants, including poverty, malnutrition, overcrowding, and population displacement driven by economic hardship and armed conflicts [3-6]. Patients often endure prolonged treatment, social isolation, stigma, and financial hardship, all of which can profoundly affect their mental health and quality of life [3-5,7]. On a global scale, TB continues to strain public health infrastructure, particularly in low- and middle-income countries, where it disproportionately affects vulnerable populations and hinders efforts toward sustainable development and health equity [2,4].

While the physical manifestations and epidemiological aspects of TB have been extensively studied, its psychological impact has received comparatively limited attention [5,7,8]. Mental health comorbidities in TB patients are not only common but also clinically significant. The chronic nature of TB, prolonged and often complex treatment regimens, along with socioeconomic challenges, collectively contribute to psychological distress. Mental disorders can lead to poor drug adherence and reduced treatment success and are recognized contributors to MDR -TB and mortality [5,7-10]. Anxiety and depression are the most frequently reported psychiatric conditions among individuals with TB, with prevalence rates substantially

higher than in the general population [7-10]. The prevalence of depression among TB patients was approximately 45%, while anxiety affects roughly 32–38% of TB patients [7-9]. Rates tend to be higher in low- and middle-income countries, where the TB burden is greatest and access to mental health care is limited [4,7,9].

Several demographic and clinical risk factors have been identified as contributing to higher psychological distress in TB patients. Female sex, older age, and low socioeconomic status have been consistently associated with higher rates of depression and anxiety [7,9-12].

Patients with multidrug-resistant TB (MDR-TB) report significantly more severe psychiatric symptoms, likely due to prolonged treatment, increased physical side effects, and poorer prognosis [10-12]. Co-infection with HIV, substance use disorders, and a prior psychiatric history further increase the likelihood of developing mental health complications [10-13]. Importantly, mental health symptoms often go unrecognized and untreated in TB patients, partly due to the overlap between somatic symptoms of TB (e.g., fatigue, weight loss, sleep disturbances) and the clinical manifestations of depression or anxiety [5,7,13]. Additionally, stigma associated with both TB and mental illness may discourage patients from seeking help, perpetuating a cycle of neglect and adverse health outcomes [7,9,13].

Recognizing and addressing mental health concerns in TB care is essential for achieving optimal health outcomes. However, mental health services are often inaccessible in many TB-endemic settings, further exacerbating the problem [4,7,14].

This review aims to explore the prevalence, pathophysiology, impact, and management of anxiety and depression in patients with TB, with a focus on integrating mental health support into routine TB care [7,14,15].

Methodology

Literature search

A comprehensive literature search was conducted to identify relevant studies addressing prevalence, pathophysiology, and management of anxiety and depression in patients with tuberculosis. The electronic databases PubMed/MEDLINE and Google Scholar were systematically searched.

The search strategy included combinations of the following keywords and Medical Subject Headings (MeSH) terms: “tuberculosis”, “TB”, “anxiety”, “depression”, “social determinants”, “comorbidity”.

The search was limited to English-language articles published between January 2000 and December 2025. Only peer-reviewed articles, reviews, and relevant policy-oriented publications were considered. Abstracts, conference proceedings, and non-peer-reviewed sources were excluded unless deemed highly relevant to the study context.

Tuberculosis, Depression, and Anxiety: Biological Link

Chronic infection with *M. tuberculosis* provokes sustained immune activation—especially IL-6 and TNF-α [16,17]. These cytokines can influence the central nervous system either by crossing the blood–brain barrier or through indirect signaling pathways, leading to neuroinflammation and altered brain function. Neuroinflammatory processes have been shown to disrupt neural circuits involved in mood regulation, particularly in the hippocampus, amygdala, and prefrontal cortex, thereby increasing vulnerability to depression and anxiety [18,19]. In parallel, persistent inflammation and disease-related stress contribute to dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis. Abnormal cortisol secretion and impaired feedback inhibition of the HPA axis are frequently observed in individuals with depressive and anxiety disorders. In patients with TB, prolonged activation of this stress-response system may exacerbate emotional dysregulation and impair adaptive coping mechanisms [2,12,13]. Another key biological pathway involves inflammation-induced alterations in tryptophan metabolism. Proinflammatory cytokines activate the enzyme indoleamine 2,3-dioxygenase (IDO), which shifts tryptophan metabolism away from serotonin synthesis toward the kynurenine pathway. This results in reduced serotonin availability and increased production of neuroactive kynurenine metabolites, some of which exert neurotoxic effects. These changes have been strongly implicated in the pathophysiology of depression and anxiety in chronic inflammatory conditions, including TB [13-15,18]. Numerous studies have shown that individuals with pulmonary tuberculosis also exhibit cognitive as well as behavioral and mood alterations; however, the number of studies elucidating the underlying pathophysiological mechanisms remains limited. Lara-Espinosa *et al.* conducted a study in mice infected with progressive pulmonary tuberculosis in the absence of neuroinfection. They found elevated levels of inflammatory cytokines in brain regions such as the hypothalamus, hippocampus, and cerebellum, accompanied by significant dysregulation of neurotransmitter synthesis (TNF-α, interleukin-12, IDO, TGF-β, interleukin-4) [20].

Additional contributors include disease-related hypoxia, malnutrition, and metabolic stress, all of which may negatively affect central nervous system function. Moreover, certain anti-tuberculosis medications, such as isoniazid and cycloserine, have been associated with neuropsychiatric side effects, potentially further increasing the risk of depressive and anxiety symptoms, but that would be further discussed in the following chapter [21,22]. Collectively, these biological mechanisms highlight a bidirectional relationship between TB and mental health disorders. Depression and anxiety may not only arise as consequences of TB-related biological processes but can also adversely affect immune function, treatment adherence, and overall disease outcomes. Understanding these shared biological pathways underscores the importance of integrating mental health assessment and care into comprehensive TB management strategies.

Pharmacological Treatment of Tuberculosis and Its Relationship with Depression and Anxiety

Pharmacological treatment of tuberculosis (TB), while essential for disease control and cure, has been associated with a range of neuropsychiatric adverse effects, including depression and anxiety. These effects may arise through direct neurochemical mechanisms, indirect metabolic pathways, and drug–drug interactions, particularly in patients with pre-existing vulnerabilities to mental health disorders.

Among first-line anti-tuberculosis medications, isoniazid has been most frequently associated with psychiatric symptoms. Isoniazid interferes with pyridoxine (vitamin B6) metabolism, which is essential for the synthesis of neurotransmitters such as serotonin, dopamine, and γ-aminobutyric acid (GABA). Pyridoxine deficiency can therefore result in mood disturbances, irritability, anxiety, and depressive symptoms. Although pyridoxine supplementation is routinely recommended, subclinical deficiency may still contribute to neuropsychiatric manifestations. In the systematic review of isoniazid-induced psychosis, daily doses of isoniazid ranged from 150 mg to 600 mg, with a median onset of psychotic and other neuropsychiatric symptoms around 15 days after treatment initiation; these findings emphasize that clinicians should remain vigilant for early neuropsychiatric adverse events across commonly used dose ranges, particularly during the first two months of therapy [23]. To date, there are no published studies specifically evaluating the dose reduction of isoniazid in patients who develop newly diagnosed depression during TB treatment.

Cycloserine, commonly used in multidrug-resistant TB regimens, is strongly associated with neuropsychiatric toxicity. As a partial agonist of the N-methyl-D-aspartate (NMDA) receptor, cycloserine can induce symptoms ranging from anxiety and depression to psychosis and suicidal ideation. The risk is dose-dependent and may be exacerbated by renal impairment, older age, and a prior history of psychiatric illness. In a cohort conducted by Court *et al.*, 136 MDR-TB patients treated with cycloserine-containing regimens, 12.5 % experienced at least one neuropsychiatric adverse event, including symptoms of depression and anxiety, most commonly within the first four weeks of treatment, highlighting a drug-associated risk for mood disturbances during anti-TB therapy [24,25]. Another study conducted by Cheng *et al.* monitored cycloserine peak plasma concentrations in patients with MDR-TB. They found that higher cycloserine peak plasma levels significantly increased

Table 1. Anti-tuberculosis drugs and psychiatric adverse effects.

Drug / Class	Cns Mechanism	Psychiatric Manifestations	Risk Factors	Clinical Recommendations
Cycloserine / Terizidone	Partial NMDA agonist → ↑ excitation, ↓ GABA	Anxiety, depression, irritability, insomnia, psychotic episodes	High serum levels (>35 μg/mL), MDR-TB regimens, no B6	Mandatory pyridoxine; dose reduction or discontinuation if symptoms occur
Ethionamide / Prothionamide	MAO inhibition → altered serotonin and dopamine	Depression, emotional lability	Long-term therapy, pre-existing depression	Monitor mood; consider switching drug
Isoniazid (Inh)	Disrupts B6-dependent neurotransmitter synthesis	Anxiety, irritability, insomnia	B6 deficiency, older age, psychiatric history	B6 supplementation; caution with antidepressants
Fluoroquinolones (Levofloxacin, Moxifloxacin)	GABA-A antagonism → ↑ excitation	Anxiety, agitation, insomnia	Elderly, CNS stimulation	Monitor neuropsychiatric symptoms
Linezolid	Reversible MAOI	Anxiety, agitation, serotonin syndrome	SSRIs/SNRIs/TCAs co-administration	Avoid serotonergic combinations; educate on early symptoms
Rifampicin	CYP3A4/CYP2C induction → ↓ antidepressant levels	Worsening depression	SSRI/TCA/BZD therapy	Monitor antidepressant efficacy; adjust dose
Isoniazid (Interactions)	CYP inhibition → ↑ antidepressant levels	AD toxicity (anxiety, agitation)	High dose, CYP substrate combinations	Reduce antidepressant dose if needed
Mdr-Tb Regimens	High psychosocial burden	Depression, anxiety, isolation	Prolonged therapy, stigma	Routine PHQ-9/GAD-7 screening; psychosocial support

the risk of neuropsychiatric toxicity, particularly when concentrations exceeded 30 mg/L. Additionally, a history of alcohol misuse further increased the risk. Regular monitoring of cycloserine plasma levels and assessment of alcohol use can help identify high-risk patients [26].

Other anti-TB agents, including ethionamide and fluoroquinolones, have also been implicated in mood and anxiety disturbances, although less consistently. Fluoroquinolones, in particular, may affect central nervous system excitability through GABA receptor inhibition, potentially contributing to anxiety, insomnia, and depressive symptoms [16-18]. In addition to direct pharmacological effects, anti-TB drugs may indirectly influence mental health through systemic side effects such as fatigue, gastrointestinal intolerance, hepatotoxicity, and sleep disturbances, which can exacerbate psychological distress. Long treatment duration, pill burden, and fear of adverse effects may further compound anxiety and depressive symptoms during TB therapy.

The relationship between anti-tuberculosis drugs and mental health is therefore complex and bidirectional. (Table 1.) While pharmacotherapy may precipitate or worsen depression and anxiety, untreated mental health disorders can negatively affect treatment adherence and outcomes.

In a prospective cohort of 202 newly diagnosed TB patients, the prevalence of depression at baseline was 50.5% as measured by the PHQ-9 scale, and logistic regression analysis showed that patients with depression at treatment initiation were 4.46 times more likely to experience treatment failure than patients without depression; those who remained depressed after the intensive phase of therapy had an approximately 34.5-fold higher risk of unsuccessful treatment outcome. A limitation of this prospective cohort study is that patients with multidrug-resistant tuberculosis (MDR-TB) were explicitly excluded from the analysis, as they represent a different population with longer, more toxic treatment regimens; this exclusion limits the generalizability of the findings to non-MDR TB populations [27].

Addressing the psychological aspects of tuberculosis may improve clinical outcomes, as psychotherapy provided alongside anti-TB treatment has been associated with higher adherence, improved treatment completion, and increased cure rates in a prospective controlled trial conducted in India [28].

Psychosocial Characteristics Predisposing to Depression and Anxiety

Depression and anxiety among patients with tuberculosis (TB) are also strongly influenced by multiple psychosocial factors that interact with biological and treatment-related mechanisms. These psychosocial characteristics increase vulnerability to mental health disorders both at the time of TB diagnosis and throughout the course of treatment [22,29-31]. One of the most prominent psychosocial stressors is TB-related stigma. TB is often associated with fear of contagion, social exclusion, and negative cultural beliefs, which can lead to discrimination, shame, and self-stigmatization. Stigma has been consistently linked to increased levels of depressive and anxiety symptoms, as it undermines self-esteem, social identity, and willingness to seek support or disclose illness [30,31]. Social isolation and reduced social support further contribute to psychological distress. TB patients may experience separation from family, friends, and workplaces due to prolonged treatment, hospitalization, or isolation measures. Limited emotional and practical support has been identified as a significant predictor of depression and anxiety, as social connectedness plays a critical protective role in coping with chronic illness [31,32]. Socioeconomic disadvantage is another major psychosocial determinant. TB disproportionately affects individuals living in poverty, who often face unemployment, financial instability, food insecurity, and inadequate housing. The economic burden of TB, including loss of income and treatment-related costs, generates chronic stress and feelings of helplessness, which increase susceptibility to mood and anxiety disorders.

Psychological responses to illness, such as fear of disease progression, fear of death, and uncertainty regarding treatment outcomes, are also common among TB patients. These illness-related cognitions can promote persistent anxiety, particularly during the early stages of diagnosis and in cases of drug-resistant TB, where treatment is longer and more complex.

In Ethiopia, 43.4% of TB patients reported depression and 41.5% reported anxiety, with stigma and lack of social support being major predictors [22]. Similar results were observed in Indonesia, where stigma strongly correlated with anxiety and depression [29].

Among drug-resistant TB patients, stigma is a dominant predictor of distress, with high rates of both depression and anxiety [30]. Qualitative studies highlight profound isolation and erosion of interpersonal relationship networks due to perceived

contagiousness [31].

Social support has a protective effect against psychological distress. Chinese data show that social support reduces distress indirectly by mitigating stigma [32]. In the Philippines, lack of family support and fear of infection have been shown to hinder treatment adherence and worsen anxiety [33]. Gender and social context also shape psychological burden: women face gender-based stigma and dependency, whereas men experience distress related to employment loss and social identity [34,35].

Collectively, these psychosocial characteristics create a context of chronic stress that not only predisposes TB patients to depression and anxiety but may also negatively influence treatment adherence and clinical outcomes. Addressing psychosocial vulnerability through integrated mental health screening, psychosocial support, and stigma reduction interventions is therefore essential for comprehensive TB care.

Screening Tools for Depression and Anxiety in TB Patients

Given the high prevalence of anxiety and depression among patients with tuberculosis, which are frequently underrecognized and can substantially and adversely affect disease progression and long-term treatment outcomes, it is essential to implement routine mental health screening tools into everyday clinical practice and TB treatment algorithms to enable early identification of affected patients [7,13].

Effective integration requires validated, easy-to-use instruments suitable for low-resource settings [9]. Commonly used tools include the PHQ-9, HADS, BDI, GAD-7, and the Zung SAS [35-41] (Table 2).

PHQ-9 (Patient Health Questionnaire-9) is the most widely validated tool in TB programs for depression. It consists of nine items based on the DSM (Diagnostic and Statistical Manual of Mental Disorders) criteria and assesses the severity of depressive symptoms over the previous two weeks. In Peru, 45.9% of newly diagnosed TB patients scored ≥ 5, supporting its programmatic utility [36]. A multicenter Chinese study reported depression in 47.9% and anxiety in 42.6% of TB in-patients using PHQ-9 and GAD-7 (Generalized Anxiety Disorder-7) [37]. GAD-7 is a seven-item questionnaire designed to screen for generalized anxiety symptoms. It shows strong psychometric validity in TB settings, including high consistency in pulmonary TB patients in South Africa [38] and elderly TB in-patients in China [39]. HADS (Hospital Anxiety and Depression Scale) is a 14-item questionnaire divided into two subscales assessing anxiety (HADS-A) and depression (HADS-D). It is used in low and middle-income countries for effective screening, though PHQ-9 and GAD-7 are more compatible with DOT (Directly Observed Therapy) workflows [40,41]. Wang *et al* performed a cross-sectional multicenter survey of 1252 pulmonary TB patients to assess the prevalence of depressive and anxiety symptoms within this population using the PHQ-9 and HADS scales. A total of 222 (17.73%) pulmonary TB patients were found to have depressive symptoms according to the PHQ-9, and 227 (18.13%) pulmonary TB patients were found to have depressive symptoms according to the HADS. Both scales showed comparable sensitivity for identifying depression and anxiety [42].

The Zung SAS (Zung Self-Rating Anxiety Scale) scale is a self-administered instrument designed to quantify the severity of anxiety symptoms in both clinical and research settings. It evaluates psychological and somatic manifestations of anxiety, making it suitable for populations with chronic physical illness, including tuberculosis (TB). It is widely used, especially in resource-limited settings, with strong validation in Indonesian TB patients [43] and predictive relevance in TB populations in Botswana [44]. Implementing the PHQ-9 and GAD-7 within TB care pathways improves early detection and facilitates referrals for counseling and mental health treatment [7,13,40,45]. It is also essential that these screening tools be administered repeatedly throughout the entire

Table 2. Screening tools for depression and anxiety in TB patients.

Screening Tool	Primary Use	No. of Items	Cut-off for Clinical Significance	Advantages / Limitations
PHQ-9	Depression	9	≥ 10 = Moderate depression	Validated in TB settings; brief; overlaps with somatic TB symptoms
HADS	Anxiety and Depression	14 (7 + 7)	≥ 8 on each subscale	Avoids somatic symptoms; useful in medical illness; may under-detect severe cases
BDI	Depression	21	≥ 17 = Mild depression	Widely used; reliable; influenced by somatic symptoms (fatigue, sleep)
GAD-7	Anxiety	7	≥ 10 = Moderate anxiety	Brief; easy to administer; focused on GAD; not a broad anxiety measure
Zung SAS	Anxiety	20	≥ 45 = Significant anxiety	Measures subjective anxiety; validated in several TB populations; less frequently used globally

course of TB treatment to enable the detection of anxiety or depression that may develop or persist at later stages of treatment.

Clinical Implications

Anxiety and depression in TB arise from intertwined biological, psychological, and social determinants. Systematic screening using validated tools like PHQ-9, GAD-7, and SAS improves detection, supports tailored interventions, and enhances treatment adherence. In systematic reviews of mental health screening in TB patients, the PHQ-9 is the most practical tool for routine depression screening, due to its brevity, ease of administration by non-specialist staff, and good sensitivity; GAD-7 is useful alongside PHQ-9 to detect anxiety, HADS remains a valid alternative for combined assessment but is less frequently implemented in TB programs, and Zung SAS is less commonly used in routine clinical practice. Integrating mental health into TB programs is essential for improving outcomes and aligns with global End TB strategies.

Conclusions

The prevalence of depression and anxiety among patients with tuberculosis is considerably high and often goes unrecognized, which can adversely affect treatment adherence and may increase mortality rates. Therefore, it is essential to implement routine mental health screening within TB treatment programs and to further deepen our understanding of the biological, psychosocial, and clinical interplay between tuberculosis and mental health.

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Conflict of interest

No conflict of interest is declared.

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