WHO operational handbook on tuberculosis

Module 6: Tuberculosis and comorbidities

Mental health conditions

World Health Organization

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Introduction to the operational handbook

Globally, tuberculosis (TB) remains a significant cause of ill health and is a leading cause of death due to an infectious agent *(1)*. The TB epidemic is attributable to five main health-related risk factors globally, namely, diabetes mellitus (diabetes), HIV, smoking and undernutrition, and disorders due to alcohol use. The contribution of these risk factors to the global TB burden is reported annually in the *Global tuberculosis report (1)*. For this operational handbook, a health-related risk factor is defined as a condition or action that increases the risk of TB disease *(2)*. When they occur in people with TB, health-related risk factors are also considered comorbidities, and may lead to poor TB treatment outcomes, lower health-related quality of life, or other suboptimal health or social outcomes, such as increased out-of-pocket costs or TB-associated disabilities.

The impact of these risk factors for TB differs between and even within countries. Collectively, they account for just under half of the new TB episodes globally *(1)*. Other significant health-related risk factors for TB disease include silicosis and disorders due to drug use. People with TB also frequently experience other comorbidities, including pulmonary and mental health conditions and viral hepatitis *(2)*. Moreover, people with TB may develop chronic lung disease or other impairments (such as musculoskeletal or neurological), all of which require specialized care or rehabilitation during TB treatment and after TB treatment completion. People with TB may also have multiple comorbidities or health-related risk factors which require holistic people-centred care in the context of universal health coverage.

Addressing individual comorbidities, multimorbidity, TB-associated disabilities and health-related risk factors for TB are key elements of Pillar one of the End TB Strategy, which focuses on integrated patient-centred care and prevention *(3)*. The End TB Strategy emphasizes that relevant comorbidities and health-related risk factors should be routinely assessed and managed for improved TB treatment and general health outcomes.

The political declaration of the 2018 United Nations High Level Meeting on the fight against TB reaffirmed the commitment to ending the TB epidemic globally by 2030, in line with the Sustainable Development Goals *(4, 5)*. In the declaration, Member States committed to a comprehensive response that addresses TB and comorbidities, as well as social and economic determinants of the epidemic, and that protects and fulfils all people's human rights and dignity *(4)*. This commitment was echoed in the latest United Nations High Level Meeting declarations on noncommunicable diseases and on HIV in 2018 *(6)* and 2021 *(7)*, respectively, in which Member States committed to assuring integrated people-centred services for TB, HIV, noncommunicable diseases and mental health.

Although global guidance on interventions to address TB and key comorbidities exists, its uptake has been variable. This operational handbook aims to support countries in scaling up people-centred care, based on the latest WHO recommendations on TB and key comorbidities, and drawing upon additional evidence, best practices and advice from experts, garnered through WHO processes.

This operational handbook is complementary to and should be used in conjunction with the *WHO consolidated guidelines on tuberculosis. Module 6: tuberculosis and comorbidities* and it also aligns with the WHO *Framework for collaborative action on tuberculosis and comorbidities (2)*. While the consolidated guidelines summarize WHO recommendations on TB and comorbidities and the evidence and processes behind them, this operational handbook provides practical guidance to aid in the implementation of these recommendations by country programmes. The Framework provides a structure and mechanisms for establishing and strengthening collaborative action across disease programmes and with relevant sectors outside the health system for the delivery of people-centred care for TB and comorbidities. It focuses on actions in five key areas and is underpinned by six principles that are fundamental to implementation *(2)*.

Objectives

The objectives of the operational handbook are to:

- support Member States to implement and scale up WHO recommendations on TB, comorbidities and health-related risk factors for TB;
- inform the development of national TB strategic plans and other relevant health strategies, guidelines and tools on integrated people-centred care for people with TB and comorbidities; and
- contribute to high-quality people-centred care for people at risk of TB or with TB disease, and for people with comorbidities and health-related risk factors, contributing to improved health, social and economic outcomes over the longer term.

Structure and evolution

The operational handbook is a living document and will include a separate section for each of the key TB comorbidities or health-related risk factors. The first section focuses on mental health conditions, important comorbidities for people affected by TB. The second section to be added will focus on TB/HIV, followed by a section on TB and diabetes and TB and undernutrition. Content for these sections is under development and will be progressively added to the operational handbook.

Target audience

This operational handbook is intended for use by people working in ministries of health, particularly TB programmes and the relevant departments or programmes responsible for comorbidities and health-related risk factors such as HIV, diabetes and other noncommunicable diseases, mental health, lung health, undernutrition, substance use and tobacco use. The operational handbook is also targeted at relevant line-ministries, policy-makers, international technical and funding organizations, researchers, nongovernmental and civil society organizations, as well as health care workers, including specialists and community health workers who support the response to TB and comorbidities in both the public and private sectors.

Mental health conditions and substance use disorders

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Mental health conditions and substance use disorders

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Abbreviations

ASSIST	Alcohol, Smoking and Substance Involvement Screening Test
AUDIT	Alcohol Use Disorders Identification Test
GAD	generalized anxiety disorder
GAD-7	Generalized Anxiety Disorder Assessment-7
HIV	human immunodeficiency virus
MDR-TB	multidrug-resistant TB
mhGAP	Mental Health Gap Action Programme
PHQ-9	Patient Health Questionnaire-9
PM+	Problem Management Plus
PWID	people who inject drugs
SH+	Self-Help Plus
SSRIs	selective serotonin reuptake inhibitors
TB	tuberculosis
UNODC	United Nations Office for Drugs and Crime
WHO	World Health Organization

Definitions

Comorbidity: A concurrent disease or health condition in a person with TB.

Disorders due to substance use: According to the International Classification of Diseases (ICD)-11 *(8)*, the term "disorders due to substance use" refers to a group of disorders that arise from a single or repeated use of substances that have psychoactive properties, including certain medications. For the purposes of this operational handbook, "disorders due to substance use" is divided into "disorders due to alcohol use" (or "alcohol use disorders"), which refers specifically to the use of alcohol, and "disorders due to drug use" (or "drug use disorders"), which refers to the use of psychoactive substances other than alcohol and nicotine.

Mental disorder: As defined by the International Classification of Diseases 11th Revision (ICD-11) *(8)*, a mental disorder is a syndrome characterized by clinically significant disturbance in an individual's cognition, emotional regulation, or behaviour that reflects a dysfunction in the psychological, biological or developmental processes that underlie mental and behavioural functioning. These disturbances are usually associated with stress or impairment in personal, family, social, educational, occupational or other important areas of functioning.

Mental health condition: A broad term covering mental disorders and psychosocial disabilities. It also covers other mental states associated with significant distress, impairment in functioning or risk of self-harm.

People-centred services: A human rights-based approach to care that consciously adopts the perspectives of individuals, carers, families and communities as participants in, and beneficiaries of, trusted health systems that respect social preferences and are organized around the comprehensive needs of people rather than individual diseases *(9)*.

Psychosocial disability: Aligned with the Convention on the Rights of Persons with Disabilities, psychosocial disability is disability that rises when someone with a long-term mental impairment interacts with various barriers that may hinder their full and effective participation in society on an equal basis with others.

Tuberculosis (TB): The disease state due to *Mycobacterium tuberculosis (10)*. It is commonly referred to as "TB disease" to distinguish it from TB infection.

Tuberculosis (TB) infection: state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens with no evidence of clinically manifest active TB *(10)*.

1. Mental health conditions and substance use disorders: background and rationale

Mental disorders[1] are prevalent in all countries *(8)*. Nearly 1 billion people worldwide are living with a mental disorder, which has become the leading cause of years of living with disability. The risk factors for developing a mental disorder are multi-faceted and may include any combination of individual factors (psychological or biological), family or community factors (such as poverty or violence), and structural factors (such as inequality or environmental emergencies) *(11)*.

People affected by TB have a higher risk for mental health conditions and substance use disorders *(12, 13)*. This comorbidity negatively impacts a person's capacity to adhere to their medication and infection control practices. It can also worsen morbidity and increase risk of poor TB treatment outcomes and poor overall health-related quality of life *(14, 15)*. Studies suggest that depression may independently increase the risk for TB *(16, 17)*. Several of the anti-TB medications are associated with depression, anxiety and/or psychoses *(12, 18, 19)*, which may require either temporary or complete suspension of the suspected agent and/or initiation of adjunct psychopharmacological medication. There is an increased risk of depression, anxiety or psychoses in people with multidrug resistant TB (MDR-TB) *(20, 21)*. Disorders due to alcohol use significantly increase the risk for developing TB *(22)*. Psychological stress associated with stigma and discrimination may also trigger or aggravate mental health conditions or substance use disorders in affected individuals. Individuals with drug-resistant TB *(23)* and/or co-infected with HIV are at an even higher risk for mental health conditions including substance use disorders *(24)*.

Many individuals with TB – and particularly those affected with drug-resistant TB – experience some degree of mental distress related to the illness, its treatment and complications, and/or TB-related stigma *(25)*. In some cases, distress, which is not always a pathological issue, can be alleviated through preventive interventions such as health education or by providing access to social and financial resources, as described below.

[1] A mental disorder - as defined by the International Classification of Diseases 11th Revision (ICD-11), is a syndrome characterized by clinically significant disturbance in an individual's cognition, emotional regulation, or behaviour that reflects a dysfunction in the psychological, biological or developmental processes that underlie mental and behavioural functioning. These disturbances are usually associated with stress or impairment in personal, family, social, educational, occupational or other important areas of functioning. This section will use 'mental disorder' when explicitly referring to data that rely on defined categories of mental disorder. A mental health condition is a broad term covering mental disorders and psychosocial disabilities. It also covers other mental states associated with significant distress, impairment in functioning or risk of self-harm. The term 'mental health conditions' will be used throughout this section except when describing data which rely on defined mental disorder categories.

For some people, however, the distress can become severe and persistent, leading to significant functional impairment or disability (such as inability to work, study or take care of family members, interpersonal strain and withdrawal from social connections) and a diagnosis of a mental disorder may be appropriate *(26)*. In addition, people already living with mental health conditions may experience a worsening of their symptoms upon diagnosis of TB. Sustained autonomic and neuroendocrine responses associated with chronic psychological distress can weaken the immune system, as well as influence health behaviours that can jeopardize TB treatment *(17)*. Since TB often affects people who are already socially vulnerable, TB-related stigma can intersect with and exacerbate other social stigmas related to poverty, mental health conditions and/or HIV co-infection, substance use, incarceration or use of social protection services. Issues created by diagnosis or treatment, such as loss of regular income, can worsen a person's mental health. TB-related stigma and discrimination can have significant deleterious impact on the physical and mental health of individuals with drug-resistant TB and may trigger mental health conditions in individuals without a history of mental health conditions *(17, 25)*. Prevention, early identification, monitoring and treatment of mental health conditions and substance use disorders are essential to ensure both alleviation of mental health conditions and positive TB treatment outcomes *(27)*.

2. People-centred care for mental health conditions and substance use disorders in people affected by TB

TB disproportionately affects people living in poverty and other socially vulnerable populations, which amplifies their risk for mental health conditions. Providers of TB care can undertake various actions to influence both the impact of disease-specific triggers on poor mental health and social determinants of mental health. In particular, social support, including education and facilitating access to psychological and material support, is critical to mitigate the impact of poverty, TB, its treatment, and the related stigma and discrimination, on people's mental health *(28)*. For individuals experiencing significant financial strain and/or food insecurity *(29)*, among other vulnerabilities, social protection interventions may mitigate stress and help prevent mental health conditions or substance use disorders *(28)*. Effective interventions to prevent and mitigate TB stigma and discrimination at the community level can help people to understand and cope with the impact of the disease.

3. Identifying and managing care for mental health conditions and substance use disorders in people affected by TB

Mental health care is one of the health services to be integrated with TB services as outlined in the End TB Strategy and the WHO *Framework for collaborative action on tuberculosis and comorbidities (2, 30)*. Within health care services, this integration includes identifying people with TB who are experiencing comorbid mental health or substance use conditions, and upon identification, managing the needs of the person – which can be achieved through referral to existing mental health or substance use services, or through task shifting to primary care health workers who have been trained in the assessment and management of mental disorders.

Key mental health conditions affecting individuals with TB are depression, anxiety, psychosis, substance use disorders and suicidal behaviours. TB diagnosis, illness course, treatment and/or stigma and discrimination, inflate the likelihood of each of these. Table 1 shows the common presentations of these conditions, and that many symptoms of mental health conditions overlap with those of TB or the side effects of TB treatment. The annex lists WHO guidance available to address these conditions.

Ideally, everyone with TB should be assessed for the above-mentioned mental health conditions or substance use disorders prior to or upon initiating treatment for TB, and at routine assessments. However, the availability of services for mental health and substance use in most countries remains largely inadequate – in some countries the treatment gap for severe mental health conditions is up to 90% *(11)*. For this reason, opportunistic identification may be a prudent use of existing resources: health workers can initiate identification when a person accessing TB care appears with signs of the common presentations of mental disorders (see Table 1). Identification can be achieved through use of screening tools for mental health and substance use.

Several standardized instruments (discussed in more detail within this guidance) are available in many languages, are easy and fast to administer, and have been widely used across diverse settings (see Table 1). As screening instruments offer information on the severity of a person's symptoms, rather than whether or not they meet diagnostic status, they can be used to identify people in need of further assessment (by a person trained in assessment of mental disorders) and/or detect changes in symptoms over time. Additionally, people at the end of anti-TB treatment may also be assessed for mental health conditions or substance use disorders. If mental health conditions or substance use disorders are present, linking people to mental health care may be important to prevent loss to follow-up during treatment, or to continue care after being discharged from the TB programme.

Ensuring TB services have referral pathways to available mental health services is an essential aspect of integrating services. Yet, task-sharing with primary health care providers has been shown to help reduce the treatment gap and increase coverage for priority mental health conditions. WHO has developed a series of guidelines and materials to inform the management of mental disorders in non-

specialized primary care settings *(31-34)*. Under the WHO Mental Health Gap Action Programme (mhGAP), the WHO *mhGAP Intervention Guide for mental, neurological and substance use disorders (32)* provides evidence-based guidance and capacity building tools for health professionals and settings not specialized in providing mental health care. Non-specialist health workers (such as those serving TB populations) can be trained in the identification, assessment, management and follow-up of priority mental health conditions. Table 1 presents an overview of priority mental health conditions and their common presentations. Additional guidance is also available for specific conditions or situations, such as the WHO/UNODC *International Standards for the Treatment of Drug Use Disorders (35)*, WHO *Guidelines for identification and management of substance use and substance use disorders in pregnancy (36)*, and the WHO guidelines on *Community management of opioid overdose (37)*.

Table 1. Overview of priority mental health conditions

Adapted from WHO mhGAP *Intervention Guide 2.0 (32)*	
• These common presentations indicate the need for assessment by persons trained in assessment, management and follow-up of these conditions, such as health workers trained in mhGAP. • If people present with features of more than one condition, then all relevant conditions need to be assessed. • All conditions apply to all ages, unless otherwise specified. • For emergency presentations (such as, but not limited to: imminent risk of self-harm/suicide, agitated or aggressive behaviour, acute alcohol intoxication), see page 18: Emergency Presentations of Priority Mental, Neurological and Substance Use Conditions in WHO *mhGAP Intervention Guide 2.0 (32)*. • For full mental health assessment, management and follow up protocols, see WHO *mhGAP Intervention Guide 2.0 (32)*. • For potential drug-drug interactions between mental health and TB treatment, see WHO *Guidelines for the management of physical health conditions in adults with severe mental disorders (38)*.	
Common presentation	**Priority condition**
• Multiple persistent physical symptoms with no clear cause • Low energy, fatigue, sleep problems • Persistent sadness or depressed mood, anxiety • Loss of interest or pleasure in activities that are normally pleasurable	**Depression**
• Multiple persistent physical symptoms with no clear cause • Persistent and excessive anxiety or worry • Muscle tension • Difficulty controlling worries • Difficulty concentrating and making decisions	**Anxiety**[a]
• Marked behavioural changes; neglecting usual responsibilities related to work, school, domestic or social activities • Agitated, aggressive behaviour, decreased or increased activity • Fixed false beliefs not shared by others in the person's culture • Hearing voices or seeing things that are not there • Lack of realization that one is having mental health problems	**Psychoses**

Adapted from WHO mhGAP *Intervention Guide 2.0 (32)*	
• Appearing affected by alcohol or other substance (e.g. smell of alcohol, slurred speech, sedated, erratic behaviour) • Signs and symptoms of acute behavioural effects, withdrawal features or effects of prolonged use • Deterioration of social functioning (e.g. difficulties at work or home, unkempt appearance) • Signs of chronic liver disease (abnormal liver enzymes), jaundiced (yellow) skin and eyes, palpable and tender liver edge (in early liver disease), ascites (distended abdomen is filled with fluid), spider naevi (spider-like blood vessels visible on the surface of the skin), and altered mental status (hepatic encephalopathy) • Problems with balance, walking, coordinated movements and nystagmus • Incidental findings: macrocytic anaemia, low platelet count, elevated mean corpuscular volume • Emergency presentation due to substance withdrawal, overdose, or intoxication. Person may appear sedated, overstimulated, agitated, anxious or confused • Recurrent requests for psychoactive medications including analgesics • Injuries • Infections associated with intravenous drug use (HIV/AIDS, Hepatitis C)	**Substance use disorders**
• Extreme hopelessness and despair • Current thoughts, plan or act of self-harm/suicide, or history thereof • Any of the other priority conditions, chronic pain or extreme emotional distress	**Self-harm/suicide**

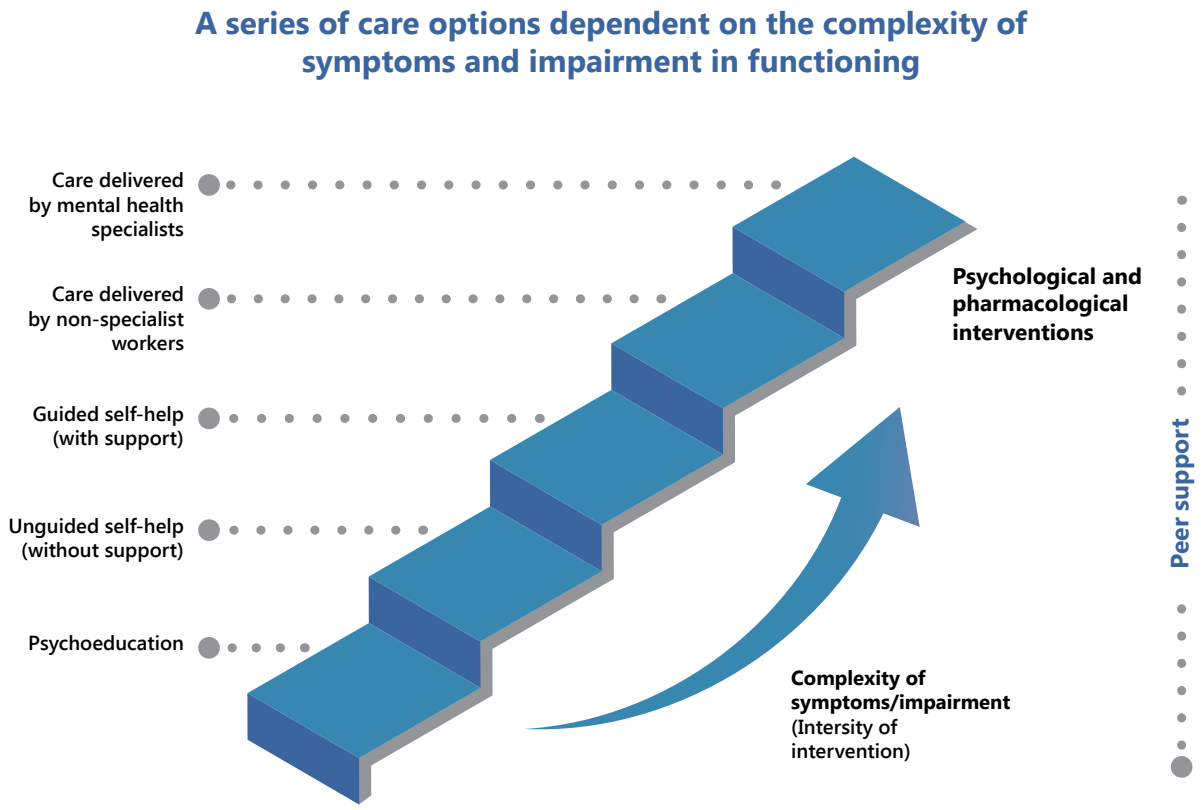
[a] Note that there are many overlapping symptoms between depression and anxiety – both of which are also referred to as common mental health conditions. The overlapping symptoms include reduced interest or pleasure in activities; significant change in appetite or weight even when food is available (decrease or increase); observable physical restlessness or retardation; irritability; unexplained physical complaints (aches, pains, muscle tension); insomnia or hypersomnia nearly every day; easily fatigued or loss of energy; difficulty concentrating or indecisiveness.

Models of delivery such as collaborative care *(39)* are also a promising approach for providing integrated evidence-based, person-centred care for mental health in physical health care settings. Collaborative care employs systematic identification of affected people, close monitoring of individual outcomes, treatment by care managers who may be trained to deliver brief educational, psychological and social interventions, and organized caseload consultations with mental health specialists, where available. Similarly, the 2022 *Framework for collaborative action on tuberculosis and comorbidities* provides guidance on how to develop and scale up collaborative action on TB and comorbidities, complementing the clinical aspects considered in this guidance *(2)*.

At the systems level, and echoing the guidance outlined within the WHO Framework for collaborative action, the WHO implementation guidance on *Integrating the prevention and control of noncommunicable diseases in HIV/AIDS, tuberculosis and sexual and reproductive health programmes* to strengthen health systems *(40)*, outlines action at multiple domain levels to benefit integration:

1. people and community, e.g. people with lived experience of the health condition must be included in planning and design of services;
2. policy and leadership, e.g. ensuring policies or legislation are in place to provide the mandate for integrated service delivery;
3. financing, e.g. health financing should support and incentivize the delivery and use of integrated care;
4. capacity and infrastructure, e.g. health workers have the necessary capacity and competencies to deliver integrated services; and
5. models of delivering integrated care give due consideration to how services should be delivered, the processes of care, and how providers and management of services are organized.

Fig. 1. Continuum of options in mental health care



At the services level, establishing person-centred, integrated TB and mental health services involves several steps. First, is the identification of opportunities for mental health support options within the local geography serving the TB community. This can include opportunities to strengthen family support and community support through, for example, a religious organization. Other opportunities might include the delivery of psychoeducation by care providers, peer supporters, trained providers of brief psychological interventions, and available mental health specialists.

One key element of people-centred care is the tailoring of interventions to the needs of individuals. In mental health care, a continuum of options is available, depending on the complexity of symptoms and associated functional impairment, as illustrated in Fig. 1. Some individuals experiencing mental health symptoms will benefit from basic psychoeducation and self-help strategies. Others may require additional support such as brief psychological interventions, which can be delivered by trained and

supervised non-specialist workers. Others may require the support of mental health specialists who deliver psychological interventions and/or pharmacological care and in the rarest circumstance they are needed, acute-care options should be available.

Next, it is necessary to strengthen linkages between the existing mental health support options and services to ensure close coordination of care. Further, TB services must establish clear protocols for identification and management of people with mental health conditions by employing screening tools, for example, or building the capacity of TB health workers to assess and manage mental disorders through WHO mhGAP *(32)*. Referral pathways can also be established with existing mental health support systems and services. Finally, robust monitoring and evaluation are needed for ongoing quality improvement.

3.1 Depression

Depression is a common and treatable mental health condition, associated with immunosuppression, which is often unrecognized and undiagnosed in individuals with TB and results in poor treatment outcomes, including treatment failure, loss to follow-up and death *(17)*.

People with depression experience a range of symptoms, including persistent depressed (or low) mood or loss of interest and pleasure, for at least two weeks, and also have considerable difficulty with daily functioning in personal, familial, social, educational, occupational or other areas *(32)*. When considering whether a person with TB has depression, it is essential to assess not only the symptoms of depression, but also difficulties in day-to-day functioning due to the symptoms, beyond those that can be attributed to TB and/or its treatment (see Table 1 and WHO *mhGAP Intervention Guide 2.0* protocol for Depression) *(32)*.

Identifying depression among individuals with TB can be difficult since some symptoms, such as marked change in appetite or weight (even when food is available), fatigue or loss of energy, and disturbed sleep, may also be commonly present in TB, thus making identification difficult. Identifying symptoms of depression can be done using screening tools such as the Patient Health Questionnaire (PHQ-9) *(41)*. Such tools do not establish a diagnosis of a mental disorder but provide an indication of the severity of symptoms. They remain a useful tool as people with symptoms of depression can be supported by lower intensity, non-pharmacological approaches, as described below. If a health worker suspects depression, a person can be referred to a health worker trained in the assessment of mental health conditions, where available, such as a mental health specialist or health worker trained in WHO mhGAP *(32)*.

Several symptoms of depression (depressed mood, diminished interest or pleasure in activities, beliefs of worthlessness or guilt and hopelessness) may be perceived as part of common reactions to TB diagnosis, stigma and discrimination, and/or worries about the likelihood of being cured. People exposed to such severe stressors often experience psychological difficulties consistent with symptoms of depression that may not necessarily meet the criteria for a diagnosis of depression *(31)*. Even so, such common reactions may cause distress, which can be mitigated through lower intensity approaches such as education or guided or unguided self-help for stress management. Initial support can also include social support to address stressors, such as for finance or housing.

In circumstances in which people demonstrate symptoms of significant distress, provision of brief psychological interventions in a stepped care approach, including guided self-help, may be warranted. If trained and supervised psychological-intervention providers are available, approaches may include

WHO Problem Management Plus (PM+) – a brief psychological intervention delivered in individual or group format for people with high distress and impaired functioning *(42)*; or WHO Self-Help Plus (SH+) – a brief guided self-help package *(43, 44)*. If symptoms of depression persist even after TB symptoms improve and external stressors have been effectively addressed through social support and social protection interventions, a referral to mental health specialists may be indicated.

Another method for identifying depression is through assessment conducted by a mental health specialist or health worker trained in such an assessment, for example following the depression protocol in the *mhGAP Intervention Guide 2.0 (32)*. This type of assessment can also be conducted following positive identification via a screening tool.

People living with depression should be regularly monitored. Management of depression should be initiated through psychosocial interventions such as psychoeducation, stress reduction, strengthening social support and promotion of daily activity functioning. Management of depression also includes offering brief evidence-based psychological interventions such as interpersonal psychotherapy, cognitive behavioural therapy, behavioural activation and problem-solving counselling, where these are available *(45)*. WHO Problem Management Plus *(42)* is a brief psychological intervention which can be delivered by trained non-mental health specialists under adequate supervision. For people with moderate to severe depression, pharmacological interventions can also be considered in the management of depression. Two recommended interventions include selective serotonin reuptake inhibitors (SSRIs), like fluoxetine, and tricyclic antidepressants like amitriptyline *(46)*. While generally safe to use among people receiving treatment for drug-susceptible TB, evidence suggests that their combination with rifampin can lead to reduced efficacy of these drugs and therefore dosing should be monitored closely. For people receiving treatment for drug-resistant TB, moderate drug-drug interactions have also been observed with levofloxacin, bedaquiline and delamanid, specifically an increased risk for QT-prolongation and/or arrhythmias *(38)*. People who experience these moderate drug interactions may use SSRIs and tricyclic antidepressants but require closer monitoring.

3.2 Anxiety

Many individuals experience symptoms of anxiety (not necessarily an anxiety disorder) as a common reaction to a TB diagnosis and the required treatment, which can often be mitigated by social support *(28, 32)*. Symptoms of anxiety in TB may present as fear of infecting others or mortality, or because of stigma and discrimination. Acute anxiety may also be an adverse reaction to a particular anti-TB agent. People with TB and symptoms of anxiety can benefit from more social support than they have in their own personal or community networks, such as peer support among other TB-affected individuals. A person-centred approach in which health workers build trust and professional rapport and increase a person's knowledge of TB and its treatment, contributes to providing a supportive environment *(47)*. As with the PHQ-9 other screening tools are available to identify whether significant symptoms of anxiety are being experienced, such as the Generalized Anxiety Disorder Assessment-7 (GAD-7) *(48)*.

If a person appears to be experiencing symptoms of anxiety that are not explained by their circumstances, and that are causing impairment in important areas of functioning, and/or that persist despite marked improvement in their physical or social environment (for example, reduced physical symptoms or increased social support), it may indicate an anxiety disorder that requires further assessment (see Table 1).

Many different anxiety- or fear-related disorders exist, such as social anxiety or panic disorders. Generalized anxiety disorder (GAD) is one type of anxiety disorder which is characterized by a generalized and persistent anxiety usually accompanied by physical symptoms such as motor tension and/or autonomic overactivity *(26)*. Anxiety symptoms in GAD must persist for more days than not, over a 6-month period, and may be focused on multiple external factors, situations or triggers.

Depending on the onset, severity, and duration of symptoms, the provider may consider (i) suspending all TB medications temporarily or (ii) suspending the suspected drug for a brief period according to the principles described in the *WHO operational handbook on tuberculosis, Module 4: Treatment - Drug-resistant tuberculosis treatment, 2022 update (49)*, and/or (iii) providing brief psychoeducation on anxiety, associated symptoms and relations to TB; offering brief training in stress management skills (e.g. mindfulness or relaxation training); offering advice on engaging in physical exercise, which can reduce symptoms of anxiety; providing brief psychological interventions based on the principles of cognitive behavioral therapy, such as PM+ or SH+, where possible and; prescribing a psychotropic medication, such as an SSRI[2] *(38)*; and offering models of collaborative care in physical disease programmes to treat comorbid TB and anxiety disorders *(50)*.

If the anxiety is associated with a drug that is part of the TB treatment regimen, any adjustment to the regimen should be done according to the principles for treatment regimen design (see *WHO operational handbook on tuberculosis, Module 4: Treatment - Drug-resistant tuberculosis treatment, 2022 update*) *(49)*. WHO is developing guidelines on the clinical management of anxiety disorders (GAD and panic disorder), as well as guidance via mhGAP for anxiety disorders.

3.3 Psychoses

People with mental disorders (such as schizophrenia, which is characterized by symptoms of psychoses) are at greater risk than the general population for exposure to infectious diseases, including TB *(51)*. Psychosis is characterized by distorted thoughts and perceptions, disturbed emotions and behaviours, and the possibility of incoherent or irrelevant speech (see Table 1). Delusions, which are fixed false beliefs not shared by others in the person's culture, are another psychosis symptom, as is hallucination – a severe alteration in the way a person perceives reality, typically exhibited as sensory experiences that do not correspond to reality, such as seeing or hearing things in the absence of an external stimulus.

In the case of drug-resistant TB, symptoms of psychoses can be triggered as a side effect of some anti-TB medications, including cycloserine, high-dose isoniazid and fluoroquinolones. Side effects resulting from anti-TB medications may include visual or auditory hallucinations, with or without delusional elaboration *(26)*. Sometimes it may present with clouding of consciousness, intellectual decline, predominant disturbance of mood, or marked delusions. In case of these presentations, it is best to refer to a mental health specialist for assessment *(26)*. In general, psychosis is best managed either by or under the supervision of a mental health specialist. Where resources are available, a baseline assessment for psychosis may be considered prior to the initiation of treatment with cycloserine, high-dose isoniazid and fluoroquinolones. This may aid providers in determining whether onset of symptoms of psychoses is associated with an anti-TB agent; and for individuals screening positive for symptoms of psychoses at baseline, close coordination between TB and mental health services is required to manage potential exacerbation of symptoms. Since the onset of psychosis as a reaction to

[2] For potential drug-drug interactions, see *WHO guidelines for management of physical health conditions in adults with severe mental disorders (38)*.

anti-TB medications is often very rapid, having a baseline assessment can help providers determine whether the symptoms may be related to a specific anti-TB agent or a mental disorder. For people with psychotic symptoms at baseline, very careful monitoring is required to ensure that these symptoms are not exacerbated by these anti-TB medications. For additional guidance, refer to the WHO *Guidelines for the management of physical health conditions in adults with severe mental disorders (38)*.

If the symptoms of psychoses do not improve after the suspected anti-TB medication has been stopped for 1–2 weeks, anti-psychotic pharmacological intervention should be considered, in consultation with a mental health specialist (see Table 1 for management of psychotic symptoms). Any adjustment to the regimen should be made according to the principles for treatment regimen design (see *WHO operational handbook on tuberculosis, Module 4: Treatment - Drug-resistant tuberculosis treatment, 2022 update*) *(49)*.

3.4 Substance use disorders

Substance use disorders (both alcohol and drug use disorders) comprise two major health conditions: "harmful substance use" and "dependence". Harmful substance use is defined as a pattern of continuous, recurrent or sporadic use of a psychoactive substance that has caused clinically significant damage to a person's physical or mental health. Dependence is defined as a disorder of regulation of psychoactive substance use arising from repeated or continuous use. The characteristic feature of dependence is a strong internal drive to use substances, which manifests itself by: (a) impaired ability to control substance use; (b) increasing priority given to substance use over other activities; and (c) persistence of use despite the occurrence of harm or negative consequences. Physiological features of dependence may also be present, including (1) increased tolerance to the effects of the substance or a need to use increasing amounts of the substance to achieve the same effect; (2) withdrawal symptoms following cessation of or reduction in the use of that substance; or (3) repeated use of the substance or pharmacologically similar substances to prevent or alleviate withdrawal symptoms.

Individuals with alcohol and other substance use disorders have a significantly higher risk for acquiring TB, TB reinfection and worse treatment outcomes *(52–54)*. According to WHO estimations, alcohol is attributable to about 20% of deaths due to TB *(55)* and according to the World Drug Report *(56)*, about 8% of people who inject drugs (PWID) have TB. Some research reports suggest even higher figures of TB prevalence among PWID, with about 17–52% testing positive on tuberculin skin testing, 60% of community-recruited PWID testing positive with interferon-gamma-release assays, and up to 68% of PWID with active TB having multidrug resistant TB *(57)*. Worse TB treatment outcomes among people with substance use and substance use disorders are often due to associated HIV infection, or viral hepatitis B and/or C, but there are other factors as well, such as worse access to treatment, stigma and discrimination, delays in seeking care, poor treatment adherence (including to HIV and TB medication), worse treatment engagement and effectiveness, compromised immune response, malnutrition, and drug-drug interactions *(52, 54)*. For potential drug-drug interactions, see WHO *Guidelines for the management of physical health conditions in adults with severe mental disorders (38)*.

Targeting substance use (both alcohol and drugs) and substance use disorders is a key strategy to prevent and treat TB *(58)*. There is evidence that treatment of substance use disorders (especially opioid agonists maintenance treatment) is associated with better initiation of and adherence to antiretroviral therapy *(59, 60)* improvements in TB treatment completion, and adherence to TB medication *(61, 62)*. However, management of substance use and substance use disorders are rarely integrated into TB and HIV care.

Due to the high comorbidity between substance use disorders and TB, it is essential to ensure access to prevention, treatment and care for both conditions. People-centred care with adequate support should be available to people with comorbid TB and substance use disorders. Health professionals providing treatment of TB should be informed and capacitated to provide basic elements of care for people with substance use disorders, including screening, providing brief intervention, recognizing and managing acute and life-threatening substance use-related conditions, and referring for specialized care when needed. Professionals working in services for mental and substance use disorders should be vigilant about comorbid TB and know how to provide care for people with both conditions.

All health professionals providing TB treatment should be able to assess and manage life-threatening conditions related to substance use, including alcohol withdrawal (complicated and not complicated with delirium and/or seizures), drug overdose and substance intoxication. Health professionals should also be able to perform screening using standardized screening tools and linked brief interventions, such as the Alcohol Use Disorders Identification Test (AUDIT) *(63)* and the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) *(33)*. For those who have difficulties in stabilizing substance use disorders while receiving treatment for TB, coordinated referral, follow-up and consultation with specialized services for mental health and substance use disorders is needed. Understanding interventions for the treatment of substance use disorders (such as harm reduction, psychosocial and pharmacological interventions, and recovery management) will help improve coordination between services and increase the effectiveness of people-centred treatment and care for people with TB and substance use disorders.

3.5 Suicidal behaviours

Over 700 000 people a year die by suicide worldwide *(64)*. One of the four key interventions in WHO's *LIVE LIFE: An implementation guide for suicide prevention in countries (65)* is the early identification of anyone affected by suicidal behaviours, and their assessment, management and follow-up. Suicidal behaviours include suicidal thoughts (or ideation), plans of suicide, suicide attempts and suicide. Individuals should be assessed for risk of self-harm/suicide prior to initiating or during TB treatment if any of the following applies: extreme hopelessness and despair, current thoughts, plan or act of self-harm/suicide or history of suicidal behaviours (e.g. thoughts, plans, acts); if a person has a comorbid mental, neurological or substance use condition (such as depression, substance use disorder, anxiety or psychosis), chronic pain or extreme emotional distress; or where cycloserine is part of the treatment regimen.

It is important to manage self-harm/suicide, including follow-up, according to the WHO mhGAP Intervention Guide 2.0, Self-Harm/Suicide protocol) *(32)*.

4. Special considerations

4.1 Stigma

Stigma refers to negative attitudes that involve discriminatory actions towards, for example, people who are receiving treatment for TB or towards those living with mental health conditions. Unfortunately, this is very common, and this stigma can result in serious violations of human rights *(66)*. Since TB and mental health conditions can affect people who are socially vulnerable, health-related stigma and discrimination can exacerbate other social stigmas which can adversely affect a person's personal, social, health and financial well-being. Health-related stigma and discrimination can have significant negative impacts on physical and mental health. Staff providing TB care should therefore be trained to avoid the use of stigmatizing language and practices related to both TB and mental health conditions. WHO's QualityRights initiative includes e-training[3] which promotes the rights of people with psychosocial, intellectual and cognitive disabilities (including mental health conditions), to address stigma, discrimination and abuse. It promotes improved quality of care in mental health and related services using a person-centred, rights-based recovery approach. The training is designed for a wide audience, including health workers.

4.2 Palliative care

Psychological support is a critical element of palliative care where the overall goal is to relieve pain and distress and sustain a person's well-being. Psychological support needs to be tailored to local settings with a culturally sensitive approach and respect for individual values and beliefs. Moreover, caregivers and health care providers providing palliative care frequently experience psychological distress themselves, for which psychological support can be beneficial *(67)*.

4.3 Homelessness

Individuals who are homeless or in temporary housing have a significantly greater risk of exposure to TB, developing active TB and acquiring drug resistance *(68)*; as well as an increased likelihood of having a mental health condition *(69)*. Assessment of their situation and related socioeconomic risk factors is required (such as poor quality or no housing, low or no income), followed by referral to the necessary support (such as social care or financial, housing or employment support). Ongoing close monitoring then is needed to provide people-centred services. Assessment for mental health conditions is also beneficial to ensure that people have access to the care they may need. These actions are important to ensure that people have improved quality of life, which can also have a positive effect on treatment outcomes.

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[3] https://www.who.int/teams/mental-health-and-substance-use/policy-law-rights/qr-e-training

4.4 Multimorbidity and TB-associated disabilities

TB often occurs along with other illnesses – not only mental disorders but also HIV, diabetes, hypertension and other conditions *(70)*. These comorbidities are also independently associated with a higher risk of mental health problems *(71)*. Health workers in TB and mental health services should endeavor to understand each person's main priorities and concerns and support the treatment of both TB and mental disorders in order to comprehensively address the person's needs. This underscores the importance of integrating mental health care and social protection in physical health care for many conditions, including TB and mental disorders.

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Annex WHO resources for mental and substance use disorders

Mental health guidelines

- Management of physical health conditions in adults with severe mental disorders: WHO guidelines *(1)*
- WHO Website: WHO Mental Health Gap Action Programme (mhGAP) *(2)*
- mhGAP Intervention Guide for mental, neurological and substance use disorders in non-specialized health settings: mental health Gap Action Programme - Version 2.0 *(3)*

Brief biological interventions

- Problem Management Plus (PM+): Individual psychological help for adults impaired by distress in communities exposed to adversity, WHO generic field-trial version 1.0. *(4)*
- Group Problem Management Plus (Group PM+): group psychological help for adults impaired by distress in communities exposed to adversity, Generic field-trial version 1.0. *(5)*
- Self-Help Plus (SH+): A group-based stress management course for adults, Generic field-trial version 1.0. *(6)*
- Group interpersonal therapy (IPT) for depression *(7)*
- Thinking healthy: A manual for psychological management of perinatal depression *(8)*

Substance use disorders

- mhGAP Intervention Guide for mental, neurological and substance use disorders in non-specialized health settings – Version 2.0 *(3)*
- The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST): manual for use in primary care *(9)*
- The ASSIST-linked brief intervention for hazardous and harmful substance use: Manual for use in primary care *(10)*
- Self-help strategies for cutting down or stopping substance use: a guide *(11)*
- International standards for the treatment of drug use disorders: revised edition incorporating results of field-testing *(12)*
- Guidelines for identification and management of substance use and substance use disorders in pregnancy *(13)*
- WHO guidelines on Community management of opioid overdose *(14)*
- Integrating collaborative TB and HIV services within a comprehensive package of care for people who inject drugs: consolidated guidelines *(15)*

Mental health integration

- Integrating the response to mental health disorders and other chronic diseases in health care systems *(16)*
- Framework for collaborative action on tuberculosis and comorbidities *(17)*

Suicide prevention

- mhGAP Intervention Guide for mental, neurological and substance use disorders in non-specialized health settings – Version 2.0 *(3)*
- LIVE LIFE: An implementation guide for suicide prevention in countries *(18)*
- Preventing suicide: A global imperative *(19)*

Mental health in emergency settings

- mhGAP humanitarian intervention guide (mhGAP-HIG): clinical management of mental, neurological and substance use conditions in humanitarian emergencies *(20)*
- Building back better: sustainable mental health care after emergencies *(21)*
- Psychological first aid: Guide for field workers *(22)*
- Mental Health and Psychosocial Support in Humanitarian Emergencies: What Should Humanitarian Health Actors Know? *(23)*
- Assessing mental health and psychosocial needs and resources: toolkit for humanitarian settings *(24)*

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