

Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders



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Contents

Acknowledgements	v
Abbreviations	vii
Glossary	ix
Executive summary	xvii
1. Introduction	2
1.1 Background and rationale	2
1.2 Aims and objectives	3
1.3 Target audience	3
1.4 Scope of the guideline	3
2. Methods	4
2.1 Contributors to the guideline	4
2.2 Declaration of interests	5
2.3 Identifying, appraising and synthesizing available evidence	5
2.4 Decision-making during the GDG meetings	9
2.5 Document preparation and peer review	9
3. Recommendations	11
3.1 Alcohol use disorders (ALC)	12
3.2 Anxiety (ANX)	18
3.3 Child and adolescent mental disorders (CAMH)	28
3.4 Conditions related to stress (STR)	46
3.5 Dementia (DEM)	50
3.6 Depression (DEP)	58
3.7 Drug use disorders (DRU)	64
3.8 Epilepsy and seizures (EPI)	76
3.9 Overarching areas (OVE)	86
3.10 Psychosis and bipolar disorder (PSY)	88
3.11 Self-harm and suicide (SUI)	108

4. Publication	112
4.1 Publication and dissemination of the guideline	112
4.2 Derivative products	112
4.3 WHO model list of essential medicines (EML)	112
5. Monitoring and evaluating the impact of the guideline	113
6. Updating the evidence	114
References	115
Annex 1. Contributors to the guideline	130
Annex 2. Managing declarations of interest and conflicts of interest	145

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Abbreviations

3WV	third wave therapies
ADHD	attention deficit hyperactivity disorder
ASM	antiseizure medicine
BAT	behavioural activation therapy
CBT	cognitive behavioural therapy
CERQual	Confidence in the Evidence from Reviews of Qualitative Research
CC	collaborative care
CI	confidence interval
DALY	disability-adjusted life-year
DBT	dialectical behaviour therapy
DLD	developmental language disorder
DOI	declaration of interest
DSM	Diagnostic and statistical manual of mental disorders
DYN	brief psychodynamic therapy
EMDR	eye movement desensitization and reprocessing
ERG	External Review Group
EtD	Evidence to Decision
GAD	generalized anxiety disorder
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluations
GRC	Guidelines Review Committee (at WHO)
HDD	heavy drinking days
iCBT	internet-based CBT
ICD	International statistical classification of diseases and related health problems
IPT	interpersonal therapy
IT	information technology
LAI	long-acting injection

LMIC	low- and middle-income country
LRT	life review therapy
mhGAP	Mental Health Gap Action Programme
MNS	mental, neurological and substance use
NGO	nongovernmental organization
NMA	network meta-analysis
NSAID	non-steroidal anti-inflammatory drug
PICO	population, intervention, comparator, outcome
PST	problem-solving therapy
PTSD	post-traumatic stress disorder
RCT	randomized controlled trial
SSRI	selective serotonin reuptake inhibitor
SMD	standardized mean difference
SUDEP	Sudden Unexpected Death in Epilepsy
SUP	supportive counselling
TAU	treatment as usual
TB	tuberculosis
TCA	tricyclic antidepressant
TEG	Topic Expert Group
WHO	World Health Organization

Glossary

Activities of daily living (ADLs)	A concept of functioning – activities of daily living are basic activities that are necessary for independent living, including eating, bathing and toileting. This concept has several assessment tools to determine an individual’s ability to perform the activity with or without assistance.
Agitation	Marked restlessness and excessive motor activity, accompanied by anxiety.
Akathisia	A subjective sense of restlessness, often accompanied by observed excessive movements (e.g. fidgety movements of the legs, rocking from foot to foot, pacing, inability to sit or stand still).
Akinesia	The absence or lack of voluntary movement. A state of difficulty initiating movements or changing from one motor pattern to another that is associated with Parkinson’s disease.
Altered mental state	A changed level of awareness or mental state that falls short of unconsciousness which is often induced by substance intake or other mental or neurological conditions. Examples include confusion and disorientation. See delirium and confusional state .
Alzheimer’s disease	A primary degenerative cerebral disease of unknown etiology in the majority of cases with characteristic neuropathological and neurochemical features. The disorder is usually insidious in onset and develops slowly but steadily over a period of several years.
Anticholinergic side-effects	Anticholinergic medicines block the effects of acetylcholine at muscarinic receptors. Anticholinergic side-effects include dryness of the mouth, urinary frequency or retention, palpitations and sinus tachycardia.
Ataxia	Failure of muscular coordination. People with ataxia have problems with coordination because parts of the nervous system that control movement and balance are affected. Ataxia may affect the fingers, hands, arms, legs, body, speech and eye movements.
Autonomy	The perceived ability to control, cope with and make personal decisions about how one lives on a daily basis, according to one’s own rules and preferences.

Note: Some of these terms are not used in this guideline document but are used in the accompanying evidence profiles, which are available [online](#).

Behavioural activation	Psychological treatment that focuses on improving mood by engaging again in activities that are task-oriented and used to be enjoyable, in spite of current low mood. It may be used as a stand-alone treatment, and it is also a component of cognitive behavioural therapy (CBT).
Bereavement	A process of loss, grief and recovery, usually associated with death.
Cerebrovascular accident	A sudden disturbance of cerebral function attributable to vascular disease, principally thrombosis, haemorrhage or embolism.
Cognitive	Mental processes associated with thinking. These include reasoning, remembering, judgement, problem-solving and planning.
Cognitive behavioural therapy (CBT)	Psychological treatment that combines cognitive components (aimed at thinking differently, e.g. through identifying and challenging unrealistic negative thoughts) and behavioural components (aimed at doing things differently, e.g. by helping the person to do more rewarding activities).
Comorbid, comorbidity	Describing diseases or disorders that exist simultaneously.
Confidentiality	Privacy in the context of privileged communication (e.g. patient–doctor consultations) and medical records is safeguarded.
Confusion, confusional state	A state of impaired consciousness associated with acute or chronic cerebral organic disease. Clinically, it is characterized by disorientation, slowness of mental processes with scanty association of ideas, apathy, lack of initiative, fatigue and poor attention. In mild confusional states, rational responses and behaviour may be provoked by examination, but more severe degrees of the disorder render the individual unable to retain contact with the environment.
Contingency management therapy	A structured method of rewarding certain desired behaviours, such as attending treatment and avoiding harmful substance use. Rewards for desired behaviours are reduced over time as the natural rewards become established.
Convulsion, convulsive movement	Clinical or subclinical disturbance of cortical function due to a sudden, abnormal, excessive and disorganized discharge of brain cells (see seizure). Clinical manifestations include abnormal motor, sensory and psychic phenomena.
Delirium	Transient fluctuating mental state characterized by disturbed attention (i.e. reduced ability to direct, focus, sustain and shift attention) and awareness (i.e. reduced orientation to the environment) that develops over a short period of time and tends to fluctuate during the course of a day. It is accompanied by (other) disturbances of perception, memory, thinking, emotions or psychomotor functions. It may result from acute organic causes such as infections, medication, metabolic abnormalities, substance intoxication or substance withdrawal.

Delusion	Fixed belief that is contrary to available evidence. It cannot be changed by rational argument and it is not accepted by other members of the person's culture or subculture (i.e. it is not an aspect of religious faith).
Detoxification	The process by which an individual is withdrawn from the effects of a psychoactive substance. Also referring to a clinical procedure, the withdrawal process is carried out in a safe and effective manner, such that withdrawal symptoms are minimized.
Disability	Any restriction or lack (resulting from an impairment) of ability to perform an activity in the manner, or within the range, considered to be normal for a human being. The term "disability" reflects the consequences of impairment in terms of functional performance and activity by the individual.
Disinhibited behaviour, disinhibition	Lack of restraint manifested in disregard for social conventions, impulsivity and poor risk assessment. It can affect motor, emotional, cognitive and perceptual aspects of a person's functioning.
Disorganized/disordered thinking	A disturbance in the associative thought process typically manifested in speech in which the person shifts suddenly from one topic to another that is unrelated or minimally related to the first. The individual gives no indication of being aware of the disconnectedness or illogicality of his or her thinking.
Disorganized behaviour	Behaviour including posture, gait and other activity that is unpredictable or not goal-directed (e.g. shouting at strangers on the street).
Distractibility	Difficulty concentrating and focusing on tasks; attention is easily diverted by extraneous stimuli.
Dystonia	Sustained muscle contraction or involuntary movements that can lead to fixed abnormal postures. See tardive dyskinesia .
Eclampsia	Any condition affecting pregnant women, characterized by seizure or convulsions newly arising in pregnancy. The condition is often associated with pregnancy-induced hypertension, convulsions, seizure, anxiety, epigastric pain, severe headache, blurred vision, proteinuria and oedema that may occur during pregnancy, labour or the puerperium.
Elevated mood	A positive mood state typically characterized by increased energy and self-esteem which may be out of proportion to the individual's life circumstances.
Extrapyramidal side-effects/symptoms (EPS)	Abnormalities in muscle movement, mostly caused by antipsychotic medication. These include muscle tremors, stiffness, spasms and/or akathisia.

Family therapy	Counselling that entails multiple (usually more than six) planned sessions over a period of months. It should be delivered to individual families or groups of families, and should include the person living with mental illness, if feasible. It has supportive and educational or treatment functions. It often includes negotiated problem-solving or crisis management work.
Fits	Colloquial term for convulsions. See convulsion .
Focal deficits	Neurological signs that are observable bodily phenomena or responses suggestive of the localization of a relatively circumscribed lesion of the nervous system.
Hallucination	False perception of reality; seeing, hearing, feeling, smelling or tasting things that are not real.
Hepatic encephalopathy	Abnormal mental state including drowsiness, confusion or coma caused by liver dysfunction.
Hyperarousal	Intense and prolonged autonomic discharge accompanied by a state of frozen watchfulness and alertness to environmental stimuli. Such responses are seen most frequently in post-traumatic stress disorders (PTSDs) and often associated with substance use or withdrawal.
Hypersensitivity reaction	Hypersensitivity reactions are adverse effects of pharmaceutical formulations (including active drugs and excipients) that clinically resemble allergy. It belongs to type B adverse drug reactions, which are defined by the World Health Organization (WHO) as the dose-independent, unpredictable, noxious and unintended response to a medicine taken at a dose normally used in humans. It covers many different clinical phenotypes with variable onset and severity.
Idiosyncratic reaction	Individual, unpredictable and non-dose-dependent response to any substance: drowsiness or euphoria, flushing, carpopedal spasms, apnoea, etc.
Informed consent	The process by which the health worker discloses appropriate information to a person who can then make a voluntary choice to accept or refuse treatment. Informed consent includes a discussion of the following elements: the nature of the decision/procedure; reasonable alternatives to the proposed intervention; the relevant risks, benefits and uncertainties related to each alternative; assessment of the person's understanding; and the acceptance of the intervention by the person.
Interpersonal therapy (IPT)	Psychological treatment that focuses on the link between depressive symptoms and interpersonal problems, especially those involving grief, disputes, life changes and social isolation. It is also known as interpersonal psychotherapy.
Irritability, irritable mood	A mood state characterized by being easily annoyed and provoked to anger, out of proportion to the circumstances.

Motivational enhancement therapy	A structured therapy (lasting up to four sessions) to help people with substance use disorders. It involves an approach to motivate change by using motivational interviewing techniques, i.e. engaging the person in a discussion about their substance use, including perceived benefits and harms in relation to the person's own values, avoiding arguing with the person if there is resistance, encouraging the person to decide for themselves what their goal may be.
Motor twitching	See convulsion .
Neuroleptic malignant syndrome (NMS)	A rare but life-threatening condition caused by antipsychotic medication, which is characterized by fever, delirium, muscular rigidity and high blood pressure.
Occupational therapy	Therapy designed to help individuals improve their independence in daily living activities through rehabilitation, exercises and the use of assistive devices. In addition, such therapy provides activities to promote growth, self-fulfilment and self-esteem.
Oppositional behaviour	Markedly defiant, disobedient, provocative or spiteful behaviour that may be manifest in prevailing, persistent angry or irritable mood, often accompanied by severe temper outbursts or in headstrong, argumentative and defiant behaviour.
Parent skills training	A family of treatment programmes that aims to change parenting behaviours and strengthen confidence in adoption of effective parenting strategies. It involves teaching parents emotional communication and positive parent-child interaction skills, and positive reinforcement methods to improve children's/ adolescents' behaviour and functioning.
Polytherapy	Provision of more than one medicine at the same time for the same condition.
Privacy	The state of being free from unsanctioned intrusion. For example, personal privacy in daily living activities (e.g. for clients in residential facilities) or confidential health records.
Problem-solving counselling	Psychological treatment that involves the systematic use of problem identification and problem-solving techniques over a number of sessions.
Pseudodementia	A disorder resembling dementia but not due to organic brain disease and potentially reversible by treatment; can manifest as symptoms of depression in some older adults.
Psychoeducation	The process of teaching people with mental, neurological and substance use (MNS) disorders and their carers/family members about the nature of the illness, including its likely cause, progression, consequences, prognosis, treatment and alternatives.

QT prolongation	A potential medication-induced side-effect of ventricular myocardial repolarization characterized by a prolonged QT interval on the electrocardiogram (ECG) that can lead to symptomatic ventricular arrhythmias and an increased risk of sudden cardiac death.
Racing thoughts	Rapid thought pattern with tangential movement from one idea to the next, often associated with mania or other mental illnesses.
Relapse	A return to drinking or other drug use after a period of abstinence, often accompanied by reinstatement of dependence symptoms. The term is also used to indicate return of symptoms of MNS disorder after a period of recovery.
Relaxation training	Involves training in techniques such as breathing exercises to elicit the relaxation response.
Respiratory depression	Inadequate slow breathing rate, resulting in insufficient oxygen. Common causes include brain injury and intoxication (e.g. due to benzodiazepines).
Respite care	Provision of temporary care in a health-care facility to a person normally cared for at home.
Rigidity	Resistance to the passive movement of a limb that persists throughout its range. It is a symptom of parkinsonism.
Seizure	Episode of brain malfunction due to disturbance of cortical function, resulting in sudden, abnormal, excessive and disorganized discharge of brain cells. Clinical manifestations include abnormal motor, sensory and psychic phenomena.
Self-harm	Intentional self-inflicted poisoning or injury, which may or may not have a fatal intent or outcome.
Serotonin syndrome	Characterized by an excess of serotonin in the central nervous system, associated with the use of various agents, including selective serotonin reuptake inhibitors (SSRIs). Serotonin syndrome may result in muscle rigidity, myoclonus, agitation, confusion, hyperthermia, hyperreflexia, as well as dysautonomic symptoms, with a risk of shock with low peripheral vascular resistance, seizures, coma, rhabdomyolysis and/or disseminated intravascular coagulation (DIC).
Slurred speech	Speech with indistinctive pronunciation.
Social network	A construct of analytical sociology referring to the characteristics of social linkages among people as a means of understanding their behaviour, rather than focusing on the attributes of individuals.
Social withdrawal	Inability of a person to engage in age-appropriate activities or interactions with his or her peers or family members.

Status epilepticus	Defined as 5 minutes or more of continuous clinical and/or electrographic seizure activity or recurrent seizure activity without recovery (returning to baseline) between seizures; it can be convulsive or non-convulsive.
Stevens-Johnson syndrome	Life-threatening skin condition characterized by painful skin peeling, ulcers, blisters and crusting of mucocutaneous tissues such as mouth, lips, throat, tongue, eyes and genitals, sometimes associated with fever. It is most often caused by a severe reaction to medications, especially antiseizure medicines.
Stigma	A distinguishing mark establishing a demarcation between the stigmatized persona and others attributing negative characteristics to this person. The stigma attached to mental illness often leads to social exclusion and discrimination and creates an additional burden for the affected individual.
Suicidal thoughts/ideation	Thoughts, ideas or ruminations about the possibility of ending one's life, ranging from thinking that one would be better off dead to formulation of elaborate plans.
Tardive dyskinesia	This is dystonia characterized by twisting and sustained muscle spasms that affect regions of the head, neck, and occasionally, the back. It may not improve after stopping the antipsychotic medicine.
Toxic epidermal necrolysis	Life-threatening skin peeling that is usually caused by a reaction to a medicine or infection. It is similar to but more severe than Stevens-Johnson syndrome.
Tremor	Trembling or shaking movements, usually of the fingers, that is an involuntary oscillation of a body part.
Valproic acid (sodium valproate)	See the <i>WHO model list of essential medicines</i> (EML). ¹ The full medicine name, “valproic acid (sodium valproate)”, is used in the recommendation text with the briefer term “sodium valproate” used in other sections of the recommendation.
Vitamin K deficiency disease of the newborn	Lack of vitamin K can cause severe bleeding in newborn babies usually immediately after birth but sometimes up to 6 months of age. Bleeding may be cutaneous, gastrointestinal, intracranial or mucosal. Maternal intake of antiseizure medicines is one of its causes.

¹ The current EML (23rd list, 2023) is available at: <https://iris.who.int/handle/10665/371090>



Executive summary

Background and objectives

Mental, neurological and substance use (MNS) disorders are major contributors to morbidity and premature mortality in all regions of the world. The resources that have been provided to tackle the huge burden of MNS disorders are insufficient, inequitably distributed and inefficiently used, resulting in a large treatment gap. To reduce the treatment gap and to enhance the capacity of countries to respond to the growing challenge, the World Health Organization (WHO) developed and launched (in 2008) the Mental Health Gap Action Programme (mhGAP): scaling up care for MNS disorders. An essential component of mhGAP is the evidence-based guideline for MNS disorders identified as conditions of high priority for low- and middle-income countries (LMICs). These recommendations were first published in 2010 as part of the mhGAP intervention guide, and they were updated in the 2015 mhGAP guideline. There has been a rapid expansion in the use of mhGAP since 2015 with the guideline and derivative products – especially the 2016 intervention guide – now used in more than 100 countries and translated into more than 20 languages.

The mhGAP guideline aims to:

- ▶ provide up-to-date WHO guidance to facilitate delivery of MNS interventions by non-specialist health workers in LMICs;
- ▶ assist with the scale-up of care for MNS disorders identified as conditions of high priority in LMICs; and
- ▶ facilitate implementation of WHO action plans including the *Comprehensive mental health action plan 2021–2030*, the *Intersectoral global action plan on epilepsy and other neurological disorders 2022–2031*, the *Global action plan on the public health response to dementia 2017–2025*, and the *Global alcohol action plan 2022–2030* by health-care planners and programme managers in LMICs.

Target audience

The guideline is targeted towards non-specialized health workers at primary- or secondary-level health-care facilities, or those working at the district level including basic inpatient and outpatient services. The guideline also targets health workers in general health care and other programmes to support delivery of integrated care and services. The guideline is relevant to other health-care professionals globally, including staff at ministries of health, nongovernmental organizations (NGOs) and researchers at academic institutions, especially in LMICs, and it is also intended for use by health-care planners, programme managers and policy-makers.

Methods

The guideline was developed in accordance with the *WHO handbook for guideline development* and meets international standards for evidence-based guidelines. In collaboration with the Guideline Development Group (GDG), the Topic Expert Groups (TEGs) and the guideline methodologist, the WHO Steering Group identified priority questions and outcomes to determine those that were critical for the development of the guideline. Conflicts of interest from all individual guideline contributors were declared, assessed and managed in line with WHO procedures. Systematic evidence reviews were used to develop the Evidence to Decision and Summary of Findings tables, according to the Grading of Recommendations Assessment, Development and Evaluations (GRADE) approach. The GDG developed recommendations that considered a range of elements, namely: the certainty of the evidence; the balance between desirable and undesirable effects; values and preferences of intended users of the intervention; resource requirements and cost-effectiveness; health equity, equality and non-discrimination; feasibility; human rights and sociocultural acceptability.

When making a strong recommendation, the GDG was confident that the desirable effects of the intervention outweighed any undesirable effects. When the GDG was uncertain about the balance between the desirable and undesirable effects, the GDG issued a conditional recommendation. **Strong recommendations** imply that most individuals would want the intervention and

should receive it, while **conditional recommendations** imply that different choices may be appropriate for different individuals, and they may require assistance to work towards a decision. The GDG members reached a unanimous agreement on all the recommendations and ratings in this guideline.

Summary of recommendations

This guideline includes 48 updated and new evidence-based recommendations related to MNS conditions. These are based on 30 updated PICO (population, intervention, comparator, outcome) questions that were included in the previous mhGAP guideline (2015), and 18 new PICO questions developed for this new edition of the guideline. For one other updated PICO question the evidence was insufficient to support an updated recommendation so the pre-existing recommendation continues to be endorsed; also for one other new PICO question there was insufficient evidence to support a new recommendation. The updated and new recommendations stand alongside

90 pre-existing guideline recommendations which were validated and continue to be endorsed in their current format.

The 48 updated and new recommendations and the 2 for which evidence was insufficient to support an updated or new recommendation are presented in Table 1, arranged among 11 modules: alcohol use disorders (ALC), anxiety (ANX), child and adolescent mental disorders (CAMH), conditions related to stress (STR), dementia (DEM), depression (DEP), drug use disorders (DRU), epilepsy and seizures (EPI), overarching areas (OVE), psychosis and bipolar disorder (PSY) and self-harm and suicide (SUI).

TABLE 1. Summary of recommendations

Module and recommendation number	Recommendation Strength of the recommendation and certainty of the evidence
Alcohol use disorders (ALC)	
ALC1 (update)	Baclofen should be considered for treatment of adults with alcohol dependence post-detoxification. Conditional recommendation. Moderate certainty of evidence.
ALC2 (update)	Structured and standardized psychosocial interventions should be considered for the treatment of alcohol dependence. Conditional recommendation. Low certainty of evidence.
ALC3 (new)	Digitally delivered interventions should be considered for adults with alcohol use disorders or with hazardous alcohol use. They should not replace provision of other forms of interventions and should ensure free and informed consent, safety, confidentiality, privacy and security. Conditional recommendation. Low certainty of evidence.

Module and recommendation number	Recommendation Strength of the recommendation and certainty of the evidence
ALC4 (new)	<p>Combined psychosocial and pharmacological interventions should be offered for adults with alcohol dependence.</p> <p>Strong recommendation. Moderate certainty of evidence.</p>
Anxiety (ANX)	
ANX1 (new)	<p>Selective serotonin reuptake inhibitors (SSRIs) should be considered for adults with panic disorder. If SSRIs are not available, consider offering tricyclic antidepressants (TCAs). SSRIs should be considered for adults with generalized anxiety disorder (GAD).</p> <p>Conditional recommendation. Low certainty of evidence.</p>
ANX2 (new)	<p>Brief, structured psychological interventions based on principles of cognitive behavioural therapy (CBT) should be offered for adults with generalized anxiety disorder (GAD) and/or panic disorder.</p> <p>Strong recommendation. Moderate certainty of evidence.</p>
ANX3 (new)	<p>When brief, structured psychological interventions based on principles of cognitive behavioural therapy (CBT) are offered for adults with generalized anxiety disorder (GAD) and/or panic disorder, different delivery formats should be considered based on available resources as well as individual preferences, including:</p> <ul style="list-style-type: none"> • individual and/or group face-to-face; • digital/online and/or face-to-face; • guided and/or unguided self-help; • specialist and/or non-specialist. <p>Conditional recommendation. Low certainty of evidence.</p>
ANX4 (new)	<p>Stress management techniques, namely relaxation and/or mindfulness training, should be considered for adults with generalized anxiety disorder (GAD) and/or panic disorder.</p> <p>Conditional recommendation. Low certainty of evidence.</p>
ANX5 (new)	<p>Structured physical exercise should be considered for adults with generalized anxiety disorder (GAD) and/or panic disorder.</p> <p>Conditional recommendation. Very low certainty of evidence.</p>
ANX6 (new)	<p>Benzodiazepines are not recommended for the treatment of adults with generalized anxiety disorder (GAD) and/or panic disorder. For emergency management of acute and severe anxiety symptoms, benzodiazepines may be considered, but only as a short-term (3–7 days maximum) measure.</p> <p>Strong recommendation. Low certainty of evidence.</p>
ANX7 (new)	<p>Collaborative care should be considered for adults with depression and/or anxiety and physical health conditions.</p> <p>Conditional recommendation. Low certainty of evidence.</p>

TABLE 1. (continued) Summary of recommendations

Module and recommendation number	Recommendation Strength of the recommendation and certainty of the evidence
Child and adolescent mental disorders (CAMH)	
CAMH1 (update)	<p>For children 6 years old and above and adolescents who have an attention deficit hyperactivity disorder (ADHD) diagnosis, methylphenidate may be considered, provided that:</p> <ul style="list-style-type: none"> • ADHD symptoms are still causing persistent significant impairment in at least one domain of functioning (education, interpersonal relationships, occupation), after the implementation of environmental modifications in schools, at home or in other relevant settings; • a careful assessment of the child/adolescent has been conducted; • the child/adolescent and the caregivers, as appropriate, have been informed about ADHD treatment options and supported in decision-making; • methylphenidate prescription is made by, or in consultation with, a specialist. <p>Conditional recommendation. Low certainty of evidence.</p>
CAMH2 (new)	<p>2.1 Universally delivered psychosocial interventions that use curriculum-based, family-based, exercise-based methods and/or social and personal skills development to improve emotional regulation should be considered for promotion of psychosocial well-being in children.</p> <p>Conditional recommendation. Very low certainty of evidence.</p> <p>2.2 Psychosocial interventions that include cognitive behavioural therapy (CBT), psychoeducation and family-focused treatment approaches should be offered to children whose parents have mental health conditions for the prevention of depression and anxiety.</p> <p>Strong recommendation. Low certainty of evidence.</p>
CAMH3 (new)	<p>3.1 Psychosocial interventions focused on social skills training and developmental behavioural approaches should be offered to improve development, well-being and functioning in children and adolescents with autism.</p> <p>Strong recommendation. Low certainty of evidence.</p> <p>3.2 Cognitive behavioural therapy (CBT) should be offered to children and adolescents with autism with anxiety.</p> <p>Strong recommendation. Moderate certainty of evidence.</p> <p>3.3 Psychosocial interventions focused on social skills, cognitive and organizational skills training should be considered to improve development and functioning in children and adolescents with attention deficit hyperactivity disorder (ADHD).</p> <p>Conditional (social skills training, cognitive interventions) and Strong (organizational skills training) recommendation. Moderate certainty of evidence.</p>

TABLE 1. (continued) Summary of recommendations

Module and recommendation number	Recommendation Strength of the recommendation and certainty of the evidence
CAMH3 (new) (continued)	<p>3.4 Beginning-to-read interventions should be offered to improve communication and academic performance in children with disorders of intellectual development.</p> <p>Strong recommendation. Moderate certainty of evidence.</p>
	<p>3.5 Early communication interventions involving direct instruction approaches should be considered for improving expressive phonological skills and reducing stuttering for children with developmental speech disorders.</p> <p>Conditional recommendation. Very low certainty of evidence.</p>
	<p>3.6 Psychosocial interventions using cognitive learning techniques to enhance communication and social competencies should be considered for children and adolescents with neurodevelopmental disabilities.</p> <p>Conditional recommendation. Low certainty of evidence.</p>
	<p>3.7 Structured physical exercise should be considered to improve development, including social and communication development, and functioning in children and adolescents with autism.</p> <p>Conditional recommendation. Low certainty of evidence.</p>
	<p>3.8 Structured physical exercise should be considered to improve motor skills and functioning, including attention and executive functioning, and reduce anxiety and problem behaviours in children and adolescents with attention deficit hyperactivity disorder (ADHD).</p> <p>Conditional recommendation. Very low certainty of evidence.</p>
	<p>3.9 Specialized instructional techniques should be considered to improve academic performance, including writing skills, reading comprehension and maths, in children and adolescents with developmental learning disorders.</p> <p>Conditional recommendation. Very low certainty of evidence.</p>
	<p>3.10 Task-oriented instruction should be considered to improve motor skills and task performance in children with developmental coordination disorders.</p> <p>Conditional recommendation. Very low certainty of evidence.</p>
	<p>3.11 Structured physical exercise and activity should be offered to improve development outcomes, including motor skills and functioning, in children and adolescents with cerebral palsy.</p> <p>Strong recommendation. Low certainty of evidence.</p>

TABLE 1. (continued) Summary of recommendations

Module and recommendation number	Recommendation Strength of the recommendation and certainty of the evidence
CAMH4 (new)	<p>4.1 Pharmacological interventions are not recommended in children and adolescents with anxiety disorders.</p> <p>Strong recommendation. Low certainty of evidence.</p> <hr/> <p>4.2 Antidepressant medicines are not recommended for the treatment of children 12 years of age and below with depressive episode/disorder.</p> <p>Strong recommendation. Low certainty of evidence.</p> <hr/> <p>4.3 If psychosocial interventions alone prove ineffective in adolescents (13–17 years) with moderate-to-severe depression, referral to or consultation with a specialist should be offered, to undertake a more comprehensive assessment and to explore initiation of fluoxetine in combination with psychological treatments.</p> <p>Strong recommendation. Low certainty of evidence.</p>
Conditions related to stress (STR)	
STR1 (update)	<p>Psychological interventions should be considered for adults with post-traumatic stress disorder (PTSD). Namely, these include:</p> <ul style="list-style-type: none"> • individual face-to-face cognitive behavioural therapy (CBT) with a trauma focus; • group face-to-face CBT with a trauma focus; • digital/remote CBT with a trauma focus; • eye movement desensitization and reprocessing (EMDR); • stress management. <p>Conditional recommendation. Low certainty of evidence.</p>
STR2 (update)	<p>Psychological interventions should be offered for children and adolescents with post-traumatic stress disorder (PTSD). Namely, these include:</p> <ul style="list-style-type: none"> • individual face-to-face cognitive behavioural therapy (CBT) with a trauma focus; • group face-to-face CBT with a trauma focus; • eye movement desensitization and reprocessing (EMDR). <p>Strong recommendation. Moderate certainty of evidence.</p>

TABLE 1. (continued) Summary of recommendations

Module and recommendation number	Recommendation Strength of the recommendation and certainty of the evidence
Dementia (DEM)	
DEM1 (update)	<p>1.1 Psychosocial interventions – namely mindfulness-based interventions, multicomponent interventions, psychoeducation and psychotherapy/counselling – should be offered for carers of people living with dementia.</p> <p>Strong recommendation. Low certainty of evidence.</p> <hr/> <p>1.2 Respite care should be considered for carers of people living with dementia.</p> <p>Conditional recommendation. Low certainty of evidence.</p> <hr/> <p>1.3 Depression and anxiety in carers of people living with dementia should be assessed and treated in line with mhGAP recommendations for depression and anxiety.</p> <p>Strong recommendation. Low certainty of evidence.</p>
DEM2	<p>There was insufficient evidence to update the recommendation, so the existing recommendation remains valid.</p> <p>Psychological interventions – namely cognitive behavioural therapy (CBT), interpersonal therapy (IPT), structured counselling and behavioural activation therapy (BAT) – should be considered for people living with dementia and mild-to-moderate depression.</p> <p>Conditional recommendation. Low certainty of evidence.</p>
DEM3 (update)	<p>3.1 Physical activity interventions – namely physical exercise delivered 3–4 times per week for 30–45 minutes for more than 12 weeks – should be offered to people living with dementia.</p> <p>Strong recommendation. High certainty of evidence.</p> <hr/> <p>3.2 Non-pharmacological interventions – namely CBT, cognitive stimulation therapy and cognitive training (in alphabetical order) – should be considered for people living with dementia.</p> <p>Conditional recommendation. Low certainty of evidence.</p>

TABLE 1. (continued) Summary of recommendations

Module and recommendation number	Recommendation Strength of the recommendation and certainty of the evidence
Depression (DEP)	
DEP1 (update)	<p>In adults with moderate-to-severe depression, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine or sertraline (SSRIs) or amitriptyline (TCA) should be considered.</p> <p>Conditional recommendation. Very low certainty of evidence.</p>
DEP2 (update)	<p>In adults with moderate-to-severe depression who have benefited from initial antidepressant treatment, continuation of the antidepressant treatment should be considered for at least six months after remission. Treatment should be regularly monitored, with special attention to treatment adherence, change in depressive symptoms and possible adverse effects.</p> <p>Conditional recommendation. Very low certainty of evidence.</p>
DEP3 (update)	<p>Structured psychological interventions should be offered for the treatment of adults with moderate-to-severe depression, namely behavioural activation therapy (BAT), brief psychodynamic therapy (DYN), cognitive behavioural therapy (CBT), interpersonal therapy (IPT), problem-solving therapy (PST) and third wave therapies (3WV).</p> <p>Strong recommendation. Moderate certainty of evidence.</p>
DEP4 (update)	<p>In adults with moderate-to-severe depression, psychological interventions or combined treatment should be considered based on individual preferences and careful consideration of the balance of benefits and harms. Antidepressant medicine alone for adults with depression (moderate to severe) should only be considered when psychological interventions are not available. Providers should keep in mind the possible adverse effects associated with antidepressant medicines, and individual preferences.</p> <p>Conditional recommendation. Low certainty of evidence.</p>

TABLE 1. (continued) Summary of recommendations

Module and recommendation number	Recommendation Strength of the recommendation and certainty of the evidence
Drug use disorders (DRU)	
DRU1 (update)	<p>1.1 Adults using cannabis should be offered screening and brief intervention. Brief intervention should comprise at least a single session, incorporating individualized feedback and advice on reducing or stopping cannabis consumption, and the offer of follow-up care.</p> <p>Strong recommendation. Very low certainty of evidence.</p> <hr/> <p>1.2 Adults using psychostimulants should be offered screening and brief intervention. Brief intervention should comprise at least a single session, incorporating individualized feedback and advice on reducing or stopping psychostimulant consumption, and the offer of follow-up care.</p> <p>Strong recommendation. Very low certainty of evidence.</p> <hr/> <p>1.3 For adults with hazardous cannabis or psychostimulant use, or with disorders due to use of these substances who do not respond to brief interventions, referral for specialist intervention should be considered.</p> <p>Conditional recommendation. Very low certainty of evidence.</p>
DRU2 (update)	<p>Dexamphetamine, methylphenidate and modafinil are not recommended for the treatment of cocaine or stimulant use disorders due to safety concerns.</p> <p>Conditional recommendation. Low certainty of evidence.</p>
DRU3 (update)	<p>Psychosocial interventions – namely cognitive behavioural therapy (CBT) and contingency management – should be offered to adults with cocaine and stimulant dependence.</p> <p>Strong recommendation. Low certainty of evidence.</p>
DRU4 (new)	<p>Digital interventions should be considered for adults using drugs or with drug use disorders. They should not replace provision of other forms of interventions and should ensure informed consent, safety, confidentiality, privacy and security.</p> <p>Conditional recommendation. Very low certainty of evidence.</p>
DRU5 (new)	<p>Recovery-oriented services on a voluntary basis should be considered for adults with drug dependence. Namely, case management, long-term residential and continuing community care approaches, occupation-based therapies and peer support groups should be considered for recovery management of people with drug dependence.</p> <p>Conditional recommendation. Low certainty of evidence.</p>

TABLE 1. (continued) Summary of recommendations

Module and recommendation number	Recommendation Strength of the recommendation and certainty of the evidence
Epilepsy and seizures (EPI)	
EPI1 (update)	<p>In adults with established status epilepticus, i.e. seizures persisting after two doses of benzodiazepines, either intravenous fosphenytoin, intravenous phenytoin, intravenous levetiracetam, intravenous phenobarbital or intravenous valproic acid (sodium valproate) should be considered with appropriate monitoring. The choice of these medicines depends on local resources, including availability and facilities for monitoring.</p> <p>Conditional recommendation. Low certainty of evidence.</p>
EPI2 (update)	<p>In children with established status epilepticus, i.e. seizures persisting after two doses of benzodiazepines, intravenous fosphenytoin, intravenous phenytoin, intravenous levetiracetam, intravenous phenobarbital or intravenous valproic acid (sodium valproate) should be considered with appropriate monitoring. The choice of these medicines depends on local resources, including availability and facilities for monitoring.</p> <p>Conditional recommendation. Moderate certainty of evidence.</p>
EPI3 (update)	<p>3.1 Generalized onset seizures:</p> <p>Monotherapy with lamotrigine or levetiracetam, or valproic acid (sodium valproate), should be offered as first-line treatment for generalized onset seizures in men/boys and women/girls who are not of childbearing potential.</p> <p>In women and girls of childbearing potential with generalized onset seizures, lamotrigine or levetiracetam should be offered as first-line monotherapy.</p> <p>If the first monotherapy is not successful for generalized onset seizures, an alternative first-line monotherapy should be tried.</p> <p>Valproic acid (sodium valproate) is not recommended in women and girls of childbearing potential owing to the high risk of birth defects and neurodevelopmental disorders in children exposed to valproic acid (sodium valproate) in the womb.</p> <p>If lamotrigine, levetiracetam and valproic acid (sodium valproate) are not available for generalized onset seizures, monotherapy with either phenytoin or phenobarbital can be considered.</p> <p>Strong recommendation. High certainty of evidence.</p>

TABLE 1. (continued) Summary of recommendations

Module and recommendation number	Recommendation Strength of the recommendation and certainty of the evidence
EPI3 (update) (continued)	<p>3.2 Focal onset seizures:</p> <p>Monotherapy with lamotrigine or levetiracetam should be offered as first-line treatment for focal onset seizures in children and adults with epilepsy.</p> <p>If neither lamotrigine nor levetiracetam are available, then carbamazepine should be used as an alternate first-line treatment for focal onset seizures in children and adults with epilepsy.</p> <p>If the first monotherapy is not successful for focal onset seizures, an alternative first-line monotherapy should be tried.</p> <p>Lacosamide should be offered as a second-line monotherapy for focal onset seizures if none of the first-line medicines are effective.</p> <p>If antiseizure medicine monotherapy is unsuccessful in people with generalized onset seizures or focal onset seizures, prompt referral should be made to a specialist for consideration of other treatment options.</p> <p>Strong recommendation. High certainty of evidence.</p>
EPI4 (update)	<p>4.1 The efficacy of antiseizure medicines (ASMs) is not thought to differ in males and females. As such, this recommendation builds on EPI3 and focuses on the medicines that are now being preferentially recommended as therapeutic options.</p> <p>In women and girls with epilepsy who are of childbearing potential, lamotrigine or levetiracetam should be offered as first-line monotherapy for both generalized onset seizures and focal onset seizures.</p> <p>Women with epilepsy should have seizures controlled as well as possible with the minimum dose of ASMs taken in monotherapy, wherever possible.</p> <p>Valproic acid (sodium valproate) is not recommended in women and girls of childbearing potential because of potential harm to the fetus.</p> <p>Strong recommendation. Very low certainty of evidence.</p> <p>4.2 Standard breastfeeding recommendations remain appropriate for women with epilepsy taking the ASMs included in this review (phenobarbital, phenytoin, valproic acid [sodium valproate], carbamazepine, lamotrigine, levetiracetam, topiramate, lacosamide).</p> <p>Strong recommendation. Very low certainty of evidence.</p>
EPI5 (new)	<p>Nocturnal supervision should be considered for prevention of sudden unexpected death in epilepsy (SUDEP).</p> <p>Conditional recommendation. Very low certainty of evidence.</p>

TABLE 1. (continued) Summary of recommendations

Module and recommendation number	Recommendation Strength of the recommendation and certainty of the evidence
Overarching areas (OVE)	
OVE1 (new)	<p>Psychosocial interventions – namely psychoeducation using problem-solving and cognitive-behavioural approaches (either individual or family-based), self-help interventions and mutual support groups – should be considered for carers of persons with psychosis or bipolar disorder.</p> <p>Conditional recommendation. Moderate certainty (carers of persons with psychosis or bipolar disorder), very low certainty (carers of persons with substance use disorder) of evidence.</p>
Psychosis and bipolar disorder (PSY)	
PSY1 (update)	<p>1.1 Oral antipsychotic medicines – namely aripiprazole, chlorpromazine, haloperidol, olanzapine, paliperidone, quetiapine, risperidone – should be offered for adults with a psychotic disorder (including schizophrenia), carefully balancing effectiveness, side-effects and individual preference.</p> <p>Strong recommendation. Moderate certainty of evidence.</p> <hr/> <p>1.2 Clozapine should be considered for adults with a treatment-resistant psychotic disorder (including schizophrenia) under mental health specialist supervision, carefully balancing effectiveness, side-effects and individual preference.</p> <p>Conditional recommendation. Moderate certainty of evidence.</p>
PSY2 (update)	<p>Maintenance therapy with antipsychotic medicine for a minimum of 7–12 months should be offered in adults with a first episode of psychosis (including schizophrenia) in remission, carefully balancing effectiveness, side-effects and individual preference.</p> <p>Strong recommendation. Moderate certainty of evidence.</p>
PSY3 (update)	<p>Maintenance therapy with mood stabilizers or antipsychotic medicines should be considered for at least six months for adults with bipolar disorder in remission, carefully balancing effectiveness, side-effects and individual preference.</p> <p>Conditional recommendation. Low certainty of evidence.</p>
PSY4 (update)	<p>Long-acting injection (LAI) antipsychotic medicines – namely fluphenazine, haloperidol, paliperidone, risperidone and zuclopenthixol – should be considered as an alternative to oral antipsychotic medicines for adults with psychotic disorders (including schizophrenia) requiring long-term treatment, carefully balancing effectiveness, side-effects and individual preference.</p> <p>Conditional recommendation. Moderate certainty of evidence.</p>

TABLE 1. (continued) Summary of recommendations

Module and recommendation number	Recommendation Strength of the recommendation and certainty of the evidence
PSY5 (update)	<p>5.1 Oral antipsychotic medicines – namely aripiprazole, olanzapine, paliperidone, quetiapine, risperidone – should be considered under specialist supervision for adolescents with psychotic disorders (including schizophrenia), carefully balancing effectiveness, side-effects and individual preference.</p> <p>Conditional recommendation. Low certainty of evidence.</p> <hr/> <p>5.2 Clozapine should be considered for adolescents with a treatment-resistant psychotic disorder (including schizophrenia) under specialist supervision, carefully balancing effectiveness, side-effects and individual preference.</p> <p>Conditional recommendation. Low certainty of evidence.</p>
PSY6 (update)	<p>Psychotropic medicines (antipsychotic medicines, namely aripiprazole, olanzapine, quetiapine, risperidone; and mood stabilizers, namely lithium) should be considered under specialist supervision for adolescents with bipolar disorder (current episode manic), carefully balancing effectiveness, side-effects and individual preference.</p> <p>Conditional recommendation. Very low certainty of evidence.</p>
PSY7 (update)	<p>7.1 Oral antipsychotic medicines (namely aripiprazole, haloperidol, olanzapine, paliperidone or quetiapine) or mood stabilizers (namely carbamazepine, lithium, valproic acid [sodium valproate]) should be offered to adults with bipolar disorder (current episode mania), carefully balancing effectiveness, side-effects and individual preference.</p> <p>Strong recommendation. Low certainty of evidence.</p> <hr/> <p>7.2 Valproic acid (sodium valproate) should not be used in women and girls of childbearing potential, owing to the high risk of birth defects and neurodevelopmental disorders in babies in utero.</p> <p>Strong recommendation. Low certainty of evidence.</p>
PSY8 (update)	<p>8.1 Mood stabilizers (namely carbamazepine, lithium, valproic acid [sodium valproate]) or oral antipsychotic medicines (namely aripiprazole, olanzapine, quetiapine) should be considered for maintenance treatment for adults with bipolar disorder in remission, carefully balancing effectiveness, side-effects and individual preference.</p> <p>Conditional recommendation. Low certainty of evidence.</p> <hr/> <p>8.2 Valproic acid (sodium valproate) should not be used in women and girls of childbearing potential with bipolar disorder in remission, owing to the high risk of birth defects and neurodevelopmental disorders in babies in utero.</p> <p>Strong recommendation. Low certainty of evidence.</p>

TABLE 1. (continued) Summary of recommendations

Module and recommendation number	Recommendation Strength of the recommendation and certainty of the evidence
PSY9 (update)	<p>Fluoxetine, olanzapine, quetiapine, valproic acid (sodium valproate) or venlafaxine should be considered for adults with bipolar depression. If fluoxetine or venlafaxine are chosen, they should be co-administered with a mood stabilizer (namely quetiapine, olanzapine, carbamazepine, valproic acid [sodium valproate], lithium).</p> <p>Conditional recommendation. Very low certainty of evidence.</p>
PSY10 (update)	<p>Treatment based on cognitive behavioural therapy (CBT) should be considered for adults with psychotic disorders (including schizophrenia) in the acute phase of the condition where sufficient specialist support is available.</p> <p>Conditional recommendation. Moderate certainty of evidence.</p>
PSY11 (update)	<p>Psychosocial interventions – namely family interventions, family psychoeducation, psychoeducation and cognitive behavioural therapy (CBT) – should be offered to adults with psychosis (including schizophrenia) during the maintenance phase, either alone or in combination.</p> <p>Strong recommendation. Moderate certainty of evidence.</p>
PSY12 (update)	<p>Individual psychological interventions – namely cognitive behavioural therapy (CBT), family psychoeducation, medicine adherence therapy, online psychoeducation or psychoeducation – should be considered as adjunctive to pharmacological interventions in the treatment of adults with bipolar disorder in remission.</p> <p>Conditional recommendation. Low certainty of evidence.</p>
Self-harm and suicide (SUI)	
SUI1 (new)	<p>Safety planning type-interventions, i.e. interventions based on principles of safety planning which are multicomponent or supplemented with follow-up or support, can be considered.</p> <p>Conditional recommendation. Very low certainty of evidence.</p>
SUI2	<p>The evidence regarding effectiveness of stand-alone media campaigns (to raise awareness and sensitize the general public about suicide and its prevention) in reducing deaths from suicide, suicide attempts and acts of self-harm is insufficient to make a recommendation.</p>
SUI3 (new)	<p>Stand-alone digital interventions based on evidence-based interventions such as cognitive behavioural therapy (CBT), dialectical behaviour therapy (DBT), problem-solving therapy (PST) and mindfulness should be considered as support for persons with suicidal thoughts.</p> <p>Conditional recommendation. Low certainty of evidence.</p>



1. Introduction

1.1 Background and rationale

Mental, neurological and substance use (MNS) disorders are prevalent in all regions of the world and are major contributors to morbidity and premature mortality. In 2019, they caused 10.1% of all global burden of disease as measured in disability-adjusted life-years (DALYs) and 25.1% of all years lived with disability (1). The resources that have been provided to tackle the huge burden of MNS disorders are insufficient, inequitably distributed and inefficiently used (2). The result is a large treatment gap, more than 75% in many countries with low and lower middle incomes (1,3). The stigma and discrimination associated with MNS conditions further exacerbates the issues and creates additional barriers for people to seek and access care (4).

To reduce the treatment gap and to enhance the capacity of countries to respond to the growing challenge, the World Health Organization (WHO) developed the Mental Health Gap Action Programme (mhGAP) (5). mhGAP has provided health planners, policy-makers and donors with a set of clear and coherent activities and programmes for scaling up care for MNS disorders. An essential component of mhGAP is the evidence-based guideline for MNS disorders identified as conditions of high priority for low- and middle-income countries (LMICs).

mhGAP was launched in 2008 (5) and the first set of WHO recommendations was published in 2010 as part of the mhGAP intervention guide (2,6). The recommendations were updated and published in the 2015 mhGAP guideline (7,8), followed a year later by the updated intervention guide in 2016 (9). These evidence-

based guidelines were developed in accordance with the *WHO handbook for guideline development* (10). The 2015 version included 23 new and updated recommendations and nine priority conditions: depression; psychosis; bipolar disorders; epilepsy; developmental and behavioural disorders in children and adolescents; dementia; alcohol use disorders; drug use disorders; and self-harm/suicide and other significant emotional or medically unexplained complaints (7). The priority conditions were selected as they represented a large burden in terms of mortality, morbidity or disability; have high economic costs; and are often associated with violations of human rights. Additionally, as part of the scaling-up strategy of mhGAP in countries, derivative products based on mhGAP guidelines were developed.

In keeping with WHO's practice of regularly monitoring new and emerging evidence, a new edition of the mhGAP guideline is now timely. The first and second editions of the mhGAP guideline, and derivative products, have been used by more than 100 countries and translated into more than 20 languages over the past 11 years. There has been a rapid expansion in the use of the guideline since 2015. A systematic review found that 33 studies reported use of mhGAP in 2017 (11). This review was recently updated, with authors noting a substantial increase in use of mhGAP with 162 new studies published since 2018 (12).

The widespread use of mhGAP has important implications, from direct clinical care to policy and system-wide changes. The use of mhGAP also affects other health systems strengthening efforts – for example, it has had an influence on the *WHO model list of essential medicines* (known as the EML) (13).

1.2 Aims and objectives

This mhGAP guideline aims to:

- ▶ provide up-to-date WHO guidance to facilitate delivery of MNS interventions by non-specialist health workers in LMICs;
- ▶ assist with the scale-up of care for MNS disorders identified as conditions of high priority in LMICs; and
- ▶ facilitate implementation of WHO action plans including the *Comprehensive mental health action plan 2021–2030* (14), the *Intersectoral global action plan on epilepsy and other neurological disorders 2022–2031* (3), the *Global action plan on the public health response to dementia 2017–2025* (15), and the *Global alcohol action plan 2022–2030* (16) by health-care planners and programme managers in LMICs.

1.3 Target audience

This third edition will have the same target audience as the first two editions of mhGAP guidelines. It is primarily targeted towards non-specialist health workers including doctors, nurses and other cadres of health workers, at primary- or secondary-level health-care facilities, and those working at the district level including basic outpatient and inpatient services.

The guideline also targets health workers working in general health care and other programmes – such as noncommunicable diseases, HIV/TB, neglected tropical diseases, and maternal, newborn and child health – to help them deliver integrated care and services.

The guideline is relevant to other health-care professionals globally, including staff at ministries of health, international and national nongovernmental organizations (NGOs), and researchers at academic institutions, especially in LMICs.

It is also intended for use by health-care planners and programme managers in close conceptual and strategic synergy with the four WHO action plans mentioned in section 1.2 (3,14,15,16). It is intended for use by policy-makers when considering intervention packages as part of universal health coverage (UHC) benefit packages.

1.4 Scope of the guideline

This is a standard guideline. It is an update of the Mental Health Gap Action Programme (mhGAP) guideline which was last updated in 2015 (7). Ten modules reflecting the priority conditions were identified for the update process: depression (DEP); psychosis and bipolar disorders (PSY); epilepsy and seizures (EPI); child and adolescent mental disorders (CAMH); dementia (DEM); alcohol use disorders (ALC); drug use disorders (DRU); self-harm and suicide (SUI); conditions related to stress (STR); and other significant emotional and medical unexplained somatic complaints (this last one was validated but not updated). The needs for a new module for anxiety disorders (ANX) and an overarching question on carers (OVE) were also identified.

2. Methods

This document was developed using the standard procedures described in the *WHO handbook for guideline development* (10) and meets international standards for evidence-based guidelines. In summary, the development process included: (i) identifying priority questions and outcomes; (ii) retrieval of the evidence; (iii) assessment and synthesis of the evidence; (iv) formulation of the recommendations; and (v) planning for the dissemination, implementation, impact evaluation and updating of the guideline.

2.1 Contributors to the guideline

The different groups involved in the development of the guideline are described below. Further details are provided in [Annex 1](#).

2.1.1 WHO Steering Group

The guideline development process was guided and overseen by the Steering Group, which comprised staff members from the WHO Department of Mental Health and Substance Use, WHO regional advisors and staff members from a number of other WHO departments. The role of the Steering Group was to identify priority questions and outcomes, in consultation with the Topic Expert Groups (TEGs) for each module, the Guideline Development Group (GDG) and the guideline methodologist. The Steering Group also decided on composition of the proposed GDG and provided overall support to guideline development.

2.1.2 Guideline Development Group

The GDG was assembled to be a diverse group of 33 individuals with expertise in research, clinical practice, health policy and programmes, and guideline development methods relating to interventions for mental health care, and persons with lived experience. The members were identified in a way that ensured geographic and gender balance. As mhGAP is intended

for use in low-resource settings, with a focus on LMICs, the information on country income (based on World Bank categorizations) has been included to ensure that this aspect is also adequately represented in the GDG membership.

A chair and co-chair of the GDG were nominated by the Steering Group and confirmed by the members of the GDG before the start of the first meeting. The co-chair also had the role of guideline methodologist. The chair and co-chair were selected based on their previous experience chairing WHO GDGs and managing group processes, as well as their content expertise and understanding of WHO guideline development processes. The role of the GDG was to support the definition of the scope of the guideline and to examine and interpret the evidence and formulate the final recommendations during meetings, and to review the draft guideline document.

2.1.3 Topic Expert Groups

The heterogeneity of expertise required to comprehensively review these modules, which span MNS disorders, led the Secretariat to introduce Topic Expert Groups (TEGs) to assist in review of the current recommendations, and provide guidance to the Steering Group.

Ten TEGs were established with 51 external experts involved. The same members served as the TEG for both the module for alcohol use disorders and the module for drug use disorders due to the overlap of expertise in these module areas. Topic experts were identified by the eight focal points – covering 11 modules² – and the WHO Secretariat based on their expertise in the module area. The size of the TEG was informed by the scope of the module. The TEGs, together with the eight focal points, had a key role in appraising existing review questions and recommendations from the previous 2015 mhGAP guideline update, and they provided suggestions on

² Each module had one person as a focal point, but the same person was the focal point for ALC and DRU, for ANX and STR, and for EPI and OVE, such that there were eight focal points across 11 modules.

the scope of the guideline update that the WHO Secretariat then proposed for consideration by the GDG. Some members of the TEG also served on the GDG.

2.1.4 Evidence review and synthesis teams

Quantitative and qualitative evidence review and synthesis teams were selected based on their thematic and technical expertise. They assessed existing evidence and, where required, conducted new systematic reviews or updates of existing reviews, and assessed the quality of the evidence using standard systematic review and grading processes, as detailed in the *WHO handbook for guideline development* (10). In addition, WHO Collaborating Centres assisted in evidence review as well as in the synthesis and evaluation of the evidence.

2.1.5 External Review Group

Members of the External Review Group (ERG) were invited to review the draft mhGAP guideline. This included individuals with expertise in research, clinical practice, health policy and programmes, interventions for mental health care, as well as individuals with lived experience. The proposed members were identified to ensure geographic and country-level income representation and gender balance.

2.2 Declaration of interests

In accordance with the WHO procedures for declarations of interests (DOIs) (17) all members of the GDG, TEGs and ERG were asked to declare in writing any competing interests (academic, financial or other) at the time of the invitation to participate in the guideline development process.

The standard WHO DOI form was completed, signed by each expert, and sent electronically to the coordinating team prior to participation in the guideline development process.

Each member of the GDG, ERG, TEGs, systematic review teams and the guideline methodologist were asked to sign a confidentiality agreement relating to the guideline development process and outcomes, using the standard WHO confidentiality undertaking form. Biographies of proposed GDG members were also displayed on the WHO website for public consultation.

The coordinating team assessed the DOIs, curriculum vitae and short biographies received, in consultation with the Steering Group, to determine if any conflict of interest existed, and discussed its severity and management plan and prepared a note for the record. The list of declared interests and notes have been updated throughout the process to reflect any new declared interests. **Annex 2** includes a summary of declared interests of GDG and ERG members as well as details on any changes to group membership that occurred during the guideline development process.

2.3 Identifying, appraising and synthesizing available evidence

2.3.1 Appraising existing review questions and recommendations

TEG members were invited to review each current recommendation for their module as presented in the 2015 edition of the mhGAP guideline (7). This review was based on their professional knowledge and/or personal experience, with a request to provide a rationale, and references where available, to support their suggested action for each recommendation. They were asked to select one of the following four suggested actions for each current recommendation and sub-recommendation.

- ▶ **Remove.** The recommendation has been superseded and is no longer relevant. Review of the evidence is not necessary and the recommendation is deleted.
- ▶ **Validate.** The recommendation is clearly established, and it is unlikely anyone would disagree with the recommendation. A review of the evidence and decision-making process are not necessary; the recommendation should be retained unchanged.
- ▶ **Edit.** There is no change in the evidence or in the intention of the recommendation, but the precise wording needs editing.
- ▶ **Update.** New evidence synthesis is required, and the topic and new evidence synthesis need to be reviewed by the GDG with a full Grading of Recommendations Assessment, Development and Evaluations (GRADE) Evidence to Decision (EtD) procedure (this includes modifications to the strength of existing recommendations based on new evidence) (18).

The TEG were also asked to identify any new questions that should be considered. The module focal points and Secretariat then prepared a summary report and provided a suggested action for each recommendation and suggested new questions, informed by TEG discussions.

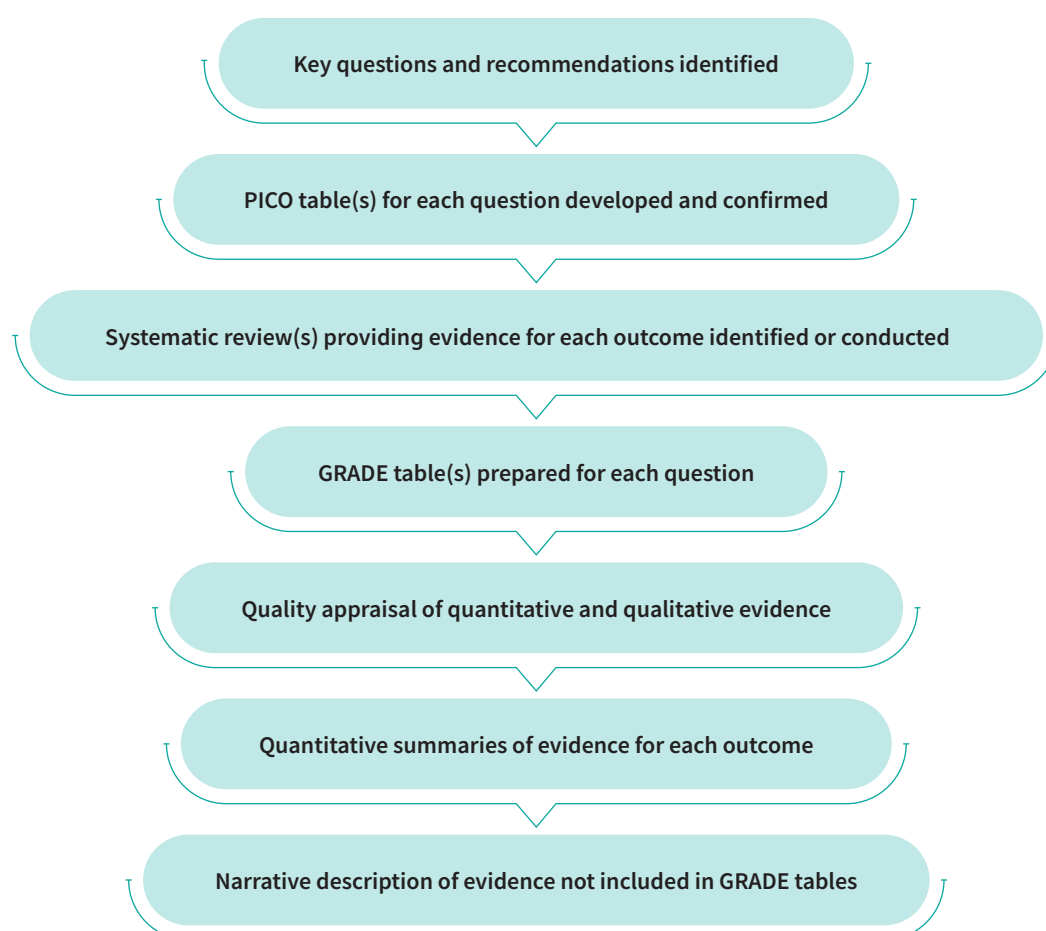
The 2015 mhGAP guideline contained 120 recommendations across 10 modules (7). The Secretariat identified the need for a new module on anxiety (ANX) based on requests from the field and in response to the growing burden of anxiety disorders (19). This module was assigned a focal point and a TEG was convened to suggest and discuss new questions

for this module. Eleven summary documents based on TEG suggestions for each module were shared with the WHO Steering Group and the GDG for their review. The Steering Group also considered whether the new questions were already covered in other WHO guidelines.

2.3.2 Appraising existing review questions and recommendations

Evidence retrieval and synthesis followed the methods outlined in the *WHO handbook for guideline development* (10), as presented in Fig. 2.1.

FIG. 2.1 The evidence retrieval, appraisal, and synthesis process for mhGAP guideline



GRADE: Grading of Recommendations Assessment, Development and Evaluations ; PICO: population, intervention, comparator, outcome.

2.3.3 Research questions

Two online scoping meetings in September 2021 with the GDG members to discuss summary documents led to 50 research questions for this update. This includes 31 updated questions based on the recommendations in the 2015 mhGAP guideline, and 19 new questions (including seven new anxiety questions). With the help of the GDG, the questions were defined using the PICO framework (population, intervention, comparator, and outcome) with critical and important outcomes specified. For updated questions, the outcomes specified in the existing 2015 mhGAP guideline (7) were used as the basis for the outcomes specified in the update and new questions.

2.3.4 Systematic review methods

Evidence to support this guideline was extracted from a number of sources by the evidence review and synthesis teams and the guideline methodologist working in collaboration with the Steering Group. Review teams developed standard protocols with clear review questions, criteria for identification of studies including search strategies for different bibliographic databases, methods for assessing risk of bias and a data analysis plan before embarking on the review. These protocols were reviewed and endorsed by the guideline methodologist, coordinating team and other members of the Steering Group, and the evidence from the reviews was retrieved according to standard operating procedures, format and timelines provided by the Steering Group. The systematic review methods used for each PICO question are detailed in the evidence profiles available [online](#).³

2.3.5 Types of evidence

Both quantitative and qualitative evidence was considered for this guideline.

Quantitative evidence

A briefing note and methodology and report templates were provided to evidence review and synthesis teams to ensure consistency across review teams. Evidence on effectiveness of interventions was mostly extracted from Cochrane Reviews and from other systematic reviews where no Cochrane Review was available. In instances where the reviews identified were found to

be out of date (i.e. the published review was more than two years old), these were updated. It is acknowledged that the COVID-19 pandemic has led to a pausing of many MNS disorder research activities over the past few years, and that this may have also impacted the availability of systematic reviews published within the preferred two-year period. For any reviews that were more than two years old, the guideline methodologist advised on suitability. New systematic reviews were conducted where there were none identified.

Regarding considerations of resources and costs, each recommendation details implementation considerations, which include information on costs where available.

Qualitative evidence

The qualitative reviews focused on what matters to end users of the interventions and health workers – in terms of barriers and facilitators to uptake of the interventions detailed in mhGAP, acceptability and feasibility of the interventions, how the interventions are valued by end users and carers, and general or specific perceptions on equity for the interventions prioritized. Evidence on the above issues was reviewed and synthesized by undertaking a qualitative review to address the questions below:

- ▶ What are end users' experiences of receiving care and treatment for MNS disorders, and what are the factors influencing the uptake of these services in LMICs?
- ▶ What are health workers' views and experiences of providing care and treatment for MNS disorders, and what are the factors influencing the provision of services in LMICs?

The qualitative evidence was also informed by two systematic reviews on the use of mhGAP, which have been published since the last update (11,12), with the most recent (2021) detailing a total of 162 peer-reviewed studies that used mhGAP. Country case studies on mhGAP implementation also informed the evidence.

The findings from the qualitative reviews, systematic reviews on the use of mhGAP, and case studies, along with quantitative reviews, provided evidence that contributed particularly to GDG discussions on the

3 <https://www.who.int/teams/mental-health-and-substance-use/treatment-care/mental-health-gap-action-programme/evidence-centre>

following domains of the GRADE EtD framework: values, health equity, equality and non-discrimination, human rights and sociocultural acceptability and feasibility.

2.3.6 Appraising evidence

Quantitative evidence

The GRADE approach to appraising the quality of quantitative evidence was used for all critical outcomes identified in the PICO questions, and a GRADE profile was prepared for each outcome within each key question. Accordingly, the certainty of evidence for each outcome was rated as “high”, “moderate”, “low” or “very low” based on the quality of the evidence (e.g. the types and sizes of studies conducted), as defined in Table 2.1. As a baseline, RCTs provide “high-

quality” evidence, while non-randomized trials and observational studies provide “low-quality” evidence. This baseline quality rating may then be downgraded based on consideration of study design limitations (risk of bias), inconsistency, imprecision, indirectness and publication bias. For observational studies, other considerations, such as magnitude of effect, could lead to upgrading of the rating if there are no limitations that indicated a need for downgrading. The systematic review teams and guideline methodologist retrieved, appraised and synthesized evidence according to the current *WHO handbook for guideline development* (10). Where possible, outcomes were presented as a meta-analysis. If this was not possible then a narrative synthesis was undertaken.

TABLE 2.1 The GRADE Quality of Evidence grading

Quality level	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Source: WHO, 2014 (10).

Qualitative evidence

The findings of the qualitative reviews were appraised for quality using the Checklist for Systematic Reviews by the Joanna Brigg’s Institute (JBI) (20). The qualitative review team used the GRADE-CERQual (Confidence in the Evidence from Reviews of Qualitative Research) tool (21,22) to assess the confidence in qualitative review findings, which was then used to assign evidence with domains on values, acceptability and feasibility, according to four components: methodological limitations of the individual studies, adequacy of data, coherence, and relevance to the review question of the individual studies that contribute to a review finding.

2.3.7 Synthesizing available evidence

For each priority question, each evidence review and synthesis team drafted the evidence summaries from relevant systematic reviews to populate the relevant sections of GRADE EtD frameworks (18). The GRADE EtD frameworks tool includes explicit and systematic consideration of evidence on interventions in terms of specified domains: priority; desirable anticipated effects; undesirable anticipated effects; certainty of the evidence of effects; balance between desirable and undesirable effects; values and preferences of intended users; resource requirements; certainty of the evidence of resource requirements; cost-effectiveness; impact on health equity, equality and non-discrimination;

implementation feasibility; and alignment with human rights principles and sociocultural acceptability. The domain “health equity, equality and non-discrimination” was informed by the findings of the qualitative systematic reviews on end users’ and health workers’ views and experiences. It was also informed by a quantitative review of the literature as provided by existing systematic reviews on use of mhGAP (11,12). The domain of “human rights and sociocultural acceptability” was informed by supporting evidence on policies and legislation for mental health and neurological disorders from WHO’s *Atlas: country resources for neurological disorders* (known as the “Neurology atlas”) (23) and WHO’s *Mental health atlas 2020* (24). “Value” placed on outcomes by persons affected by the recommendations is especially relevant to people with mental health conditions. The qualitative reviews informed this domain. “Sociocultural acceptability” (preferences of persons affected by the recommendations) relates to whether an intervention is acceptable to individuals with the MNS disorders, and to health service providers. Qualitative evidence from the systematic review on end users and health workers’ views and experiences informed judgements for this domain.

The Steering Group reviewed the evidence summaries and evidence profiles in collaboration with the evidence review and synthesis teams and guideline methodologist and presented them to the GDG in a series of meetings. The evidence profiles can be found [online](#).

2.4 Decision-making during the GDG meetings

The GDG meetings took place between June and November 2022. This included seven half-day virtual meetings, one all-day virtual meeting and five all-day hybrid meetings (with both virtual and in-person attendance).

The evidence summaries for each PICO question, and a pre-recorded evidence presentation, were provided to members of the GDG in advance of each GDG meeting. GDG members were asked to review these materials and provide any key comments in advance of the meeting.

At the meetings, under the leadership of the GDG chair, the evidence review and synthesis team presented a summary of the evidence. GDG members then came to a consensus on the rating for each element of the EtD table, providing additional information on the various domains. The draft recommendations were then formulated by the GDG. The aim of the meeting was to reach consensus on the quality of the supporting evidence and draft recommendations. The draft of each recommendation was made by consensus, defined as full agreement among all GDG participants, when possible.

In line with the *WHO handbook for guideline development* (10), two main types of recommendations were presented at the meeting, as shown in [Table 2.2](#).

No recommendation was proposed in cases where insufficient evidence was available to put forward an updated or new recommendation for a PICO under consideration.

If GDG members were unable to reach a consensus, the decision was put to a vote. A recommendation or decision stood if a large majority (more than two thirds of the participants) voted in support of it. Voting was done by a show of hands (electronic and/or physical depending on meeting format).

The WHO Steering Group, evidence review and synthesis teams, guideline methodologist and meeting observers did not participate in the voting process.

2.5 Document preparation and peer review

Following all the outlined processes, the Steering Group circulated draft recommendations to the GDG members for further comment. A full draft of the guideline document, including the recommendations and supporting evidence, was then sent to the ERG electronically for review to identify factual errors and to comment on clarity of language and considerations related to implementation, adaptation and contextual issues. The full draft was also shared with the Steering Group and GDG for any final comments. All comments from the Steering Group, GDG and ERG were collated by the coordinating team to revise the draft.

TABLE 2.2 Descriptions of strong and conditional recommendations

Audience	Strong recommendation	Conditional recommendation
For people, individuals with lived experience, the public	Most individuals in this situation would want to pursue the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want to pursue the suggested course of action, but many would not.
For health workers or delivery agents of an intervention	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Different choices will be appropriate for different people, and that each person must be helped to arrive at a management decision consistent with their values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences. Clinicians should expect to spend more time with individuals when working towards a decision.
For policy-makers	The recommendation can be adapted as policy in most situations.	Policy-making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions.

Source: adapted from WHO, 2014 (10).

3. Recommendations

This guideline includes 48 updated and new evidence-based recommendations related to MNS conditions. These are based on 30 updated PICO questions that were used for the previous mhGAP guideline (2015), and 18 new PICO questions developed for this new edition of the guideline. For one other updated research question the evidence was insufficient to support an updated recommendation so the pre-existing recommendation continues to be endorsed; also for one other new research question there was insufficient evidence to support a new recommendation. Fourteen recommendations/questions (ALC1, ALC2, ALC3, ALC4, CAMH1, STR1, STR2, DRU1, DRU3, DRU4, EPI1, EPI2, OVE1, SUI3) were

based on new/updated systematic reviews while the remaining recommendations were based on existing/previously published systematic reviews.

The 48 updated and new recommendations are presented in this chapter by module (sections 3.1–3.11). For each recommendation, the relevant justification, remarks, research gaps and implementation considerations are also presented. The evidence profiles are available [online](#).

The updated and new recommendations in this guideline stand alongside 90 pre-existing guideline recommendations which were validated and continue to be endorsed in their current format (7).



3.1 Alcohol use disorders (ALC)



ALC1. In adults with alcohol dependence post-detoxification, is baclofen effective for relapse prevention and management of alcohol dependence?

Recommendation (update):	Baclofen should be considered for treatment of adults with alcohol dependence post-detoxification.	
	Strength of recommendation:	Conditional
	Certainty of evidence:	Moderate

Justification

- A systematic review was updated: Agabio et al., 2023 (17 RCTs) (25).
- Compared with placebo, baclofen decreases the risk of relapse into any drinking at end of treatment (high certainty) and increases the percentage of days abstinent at end of treatment (moderate certainty).
- Compared with placebo, baclofen does not increase the number of participants with at least one adverse event at the end of treatment (high certainty) and does not increase the number of dropouts due to adverse events (high certainty).
- In subgroup analysis for baclofen versus placebo, for some outcomes (return to any drinking and percentage of days abstinent), baclofen showed better effectiveness for people with alcohol dependence post-detoxification (after management of withdrawal syndrome) when compared with people who are using alcohol (non-detoxified), but no differences were identified for low/high dosages or duration of treatment. For other outcomes (dropouts from treatment), duration of treatment longer than 12 weeks showed effect, but no other difference was identified for adverse events or dropouts due to adverse events for dosages, duration of treatment or detoxification status.

Remarks

- The term “alcohol dependence” refers to diagnosis according to *The ICD-10 classification of mental and behavioural disorders* (26) or the *Diagnostic and statistical manual of mental disorders* (27), 4th edition (DSM-IV) criteria or equivalent ICD-11 (28) and DSM-5 diagnosis (29).

- Post-detoxification refers to completion of the management of withdrawal symptoms at least three days before starting treatment. Most included studies required participants to abstain from alcohol for at least three days (3–28) before beginning the pharmacological treatment.
- Service providers should include appropriate psychosocial interventions in their treatment plan and should only consider medication alone for adults with alcohol dependence when psychosocial interventions are not available.

Research gaps

- The majority of the evidence is from high-income countries (HICs). Further research is needed in low- and middle-income countries (LMICs).
- All RCTs excluded participants with comorbid severe mental disorders, but five studies recruited participants under stable doses of antidepressants. Further research is required to investigate baclofen’s profile of efficacy and safety among those with comorbid severe mental disorders.
- Further evidence is required to conclude whether the balance of effects differs between baclofen and acamprosate or naltrexone.

Implementation considerations

- Baclofen is available in a generic form and is inexpensive but may not be available in all countries and is not registered for the treatment of alcohol dependence. The lack of formal approval for baclofen’s use for alcohol dependence places increased responsibility on the medical practitioner prescribing baclofen to inform

people of the risks and benefits of its use for alcohol dependence.

- Even though differences were not identified when compared with placebo, baclofen can have side-effects such as sedation, and cessation of

baclofen treatment can be associated with a mild benzodiazepine-like withdrawal syndrome. Therefore, baclofen should be reduced gradually rather than stopped abruptly with service providers monitoring for these side-effects.

ALC2. In adults with alcohol dependence, are psychosocial interventions effective?

Recommendation (update):	Structured and standardized psychosocial interventions should be considered for the treatment of alcohol dependence.	
	Strength of recommendation:	Conditional
	Certainty of evidence:	Low

Justification

- A systematic review was updated: Ghosh et al., 2023 (16 studies).⁴
- In adults with alcohol dependence, any psychosocial intervention compared with treatment as usual (TAU) shows an effect for increasing the proportion of abstinent participants/abstinence rates (low certainty).
- In adults with alcohol dependence, any psychosocial intervention compared with TAU shows little to no difference for the proportion of days abstinent (low certainty), quantity of drinks (high certainty) and frequency of drinking (high certainty) at end of treatment.
- In adults with alcohol dependence, it is uncertain if any particular type of psychosocial intervention (e.g. cognitive behavioural therapy [CBT], mindfulness-based relapse prevention, contingency management, brief intervention) is effective in comparison with TAU, as opposed to the grouped category of “any psychosocial intervention”.
- In adults with alcohol dependence, network support therapy (including Alcoholics Anonymous attendance) compared with CBT showed an effect for increasing the proportion of days of abstinence (moderate certainty).

Remarks

- The term “alcohol dependence” refers to diagnosis according to the ICD-10 or DSM-IV criteria or equivalent ICD-11 and DSM-5 diagnosis.
- Psychosocial interventions included: CBT, couples therapy, psychodynamic therapy, behavioural therapies, social network therapy, contingency management, motivational interviewing, 12-step facilitation, mutual help groups and mindfulness-based therapies. Studies were included if they considered the above treatments alone or in combination with other types of treatment. The review excluded studies on a combination of pharmacotherapy and psychosocial interventions, as well as on interventions delivered on digital platforms.
- Integrating the provision of psychosocial interventions into primary care provides many advantages, including more holistic health care, increased accessibility of services for MNS disorders for people in need of care, opportunities for reducing the stigma of mental health problems and reduced costs.

Research gaps

- The majority of studies were conducted in HICs. Further research is needed in LMICs.

⁴ Ghosh A, Morgan N, Calvey T, Scheibein F, Angelakis I, Panagioti M et al. Effectiveness of psychosocial intervention for alcohol dependence: a systematic review and meta-analysis update. 2023 (in preparation).

- All studies excluded participants with comorbid severe mental disorders, with two studies recruiting participants with common mental disorders. Further research is required to investigate the balance of effects in those with comorbid severe mental disorders.
- Further research is needed to determine whether the balance of effects differs by type of psychosocial intervention.
- Psychosocial interventions for alcohol dependence should be considered in conjunction with other modalities of treatment (i.e. pharmacological).
- Most psychosocial interventions may be delivered by a wide range of professional staff – counsellors, psychologists, nurses, lay health counsellors and health volunteers. This increases the feasibility of implementing psychosocial interventions.
- Psychosocial interventions can be delivered effectively in non-specialized health-care settings but also in other settings, including specialized mental health care and social care.

Implementation considerations

- Country adaptation and translation of training materials and tools for the provision of psychosocial interventions is essential.

ALC3. In adults with alcohol use disorders or hazardous drinking, are digital interventions effective?

Recommendation (new):	Digitally delivered interventions should be considered for adults with alcohol use disorders or with hazardous alcohol use. They should not replace provision of other forms of interventions and should ensure free and informed consent, safety, confidentiality, privacy and security.	
	Strength of recommendation:	Conditional
	Certainty of evidence:	Low

Justification

- Evidence was extracted from two systematic reviews: Sundström et al., 2017 (14 RCTs) (30); and an update of this review by Boumparis et al., 2023 (49 RCTs).⁵
- In adults with alcohol use disorders or with hazardous alcohol use, digital interventions, when compared with non-active (waitlist, assessment-only) and active TAU, brief interventions) comparators, show an effect for reducing alcohol use (low certainty).
- The included digital interventions encompass both unguided and guided digital interventions. In unguided digital interventions, psychoeducation and psychotherapeutic techniques are provided for the individual to self-manage their symptoms without the help of a health professional. In guided digital interventions, additional guidance is provided from health professionals who can assist participants with technical or health-related questions via chat, email or telephone.
- The studies assessing alcohol reduction via digital interventions compared with active comparators usually recruited individuals from specialized treatment facilities. The majority of those interventions combined the digital component with face-to-face treatments, such as TAU or CBT, and last 8–12 weeks.

Remarks

- The terms “alcohol use disorder” and “hazardous alcohol use” refer to diagnosis according to the ICD-10 or DSM-IV criteria or equivalent ICD-11 and DSM-5 diagnosis.

⁵ Boumparis N, Khazaal Y, Krupchanka D, Schaub MP. Digital interventions for problem drinkers: a systematic review and meta-analysis. 2023 (in preparation).

- Differences in findings between active/non-active comparators should be interpreted with caution. For the comparisons involving non-active comparators, the majority of individuals were recruited based on self-reported use patterns and not assessed for an alcohol use disorder. This is contrary to the studies involving active comparators, which recruited participants after the diagnosis of an alcohol use disorder. For this reason, it is important to stress that different findings for active/non-active comparators are likely due to the different characteristics (such as severity) of the target group and the intensity of the treatment provided.
- Digital interventions should not be used to replace or detract from provision of other forms of interventions.
- There are concerns regarding potentially sensitive content and data privacy while using digitally delivered health interventions. Measures should be taken to ensure that digital interventions are provided under conditions of safety/security, confidentiality, informed consent and privacy of data. This can include the establishment of standard operating procedures that describe protocols for ensuring consent, data protection and storage, and verifying provider licensing and credentials. Further guidance can be found in the 2019 *WHO guideline: recommendations on digital interventions for health system strengthening* (31).

Research gaps

- Subgroup analyses did not show significant differences between groups (guided versus unguided interventions, alcohol use disorders versus no alcohol use disorders). However, the ability to perform subgroup analyses was limited due to the small number of studies in the different conditions and types of interventions. Larger studies are required to understand these subgroup differences.
- Further individual participant data meta-analyses and network meta-analyses (NMAs) would also be of value in investigating the effectiveness of digital interventions for alcohol use disorders and

identifying important characteristics that might be associated with an improved treatment effect.

- There is not enough data to understand the role of digital interventions for equity, equality and non-discrimination of people using substances: while there is potential for increasing access to care, it is also possible that not all people can benefit due to the “digital divide”, which requires further research.

Implementation considerations

- Digitally delivered interventions can provide benefits to people with an alcohol use disorder and those with hazardous alcohol use, especially when provided in addition to TAU. Digitally delivered interventions should not substitute provision of other types of conventional treatment (psychosocial or pharmacological) to people with alcohol use disorders. When face-to-face treatment is not available or acceptable, then self-help digital interventions can be a feasible option to provide support.
- Setting up and sustaining digital health solutions can be costly, while costs for individual users are usually not very high, making implementation feasible for the end user.
- There is a need to consider the potential digital divide across population groups with some having unequal access to and skills to use digital technologies. Access might be particularly difficult for certain population groups with poor access to network services, mobile devices or electricity, and/or with low literacy and digital literacy skills. Measures should be taken to address inequities in access to mobile devices so that further inequity is not perpetuated in accessing health information and services, including mechanisms to ensure individuals who do not have access to mobile devices can still receive appropriate services.
- Country adaptation and translation of digital interventions tools with subsequent evaluation is essential.

ALC4. In adults with alcohol use disorders, are combined pharmacological and psychosocial interventions effective and safe?

Recommendation (new):	Combined psychosocial and pharmacological interventions should be offered for adults with alcohol dependence.	
	Strength of recommendation:	Strong
	Certainty of evidence:	Moderate

Justification

- Evidence was extracted from a new systematic review: Agabio et al., 2023 (14 studies) (32).
- In adults with alcohol dependence, combined treatment in comparison with psychosocial interventions alone showed an effect (at the end of treatment) for: (i) decreasing risk to return to any drinking (74 fewer per 1000; 95% CI: 132 to 16 fewer; high certainty); (ii) decreasing risk to return to heavy drinking (75 fewer per 1000; 95% CI: 1270 to 22 fewer; moderate certainty); (iii) increasing proportion of abstinent days (6.22% abstinent days more; 95% CI: 3.82% to 8.61%; high certainty); (iv) decreasing the number of drinks per drinking day (standardized mean difference [SMD] = 0.31; 95% CI: 0.5 to 0.11; high certainty).
- In adults with alcohol dependence, combined treatment in comparison with pharmacological interventions alone, showed an effect (at the end of treatment) for: (i) decreasing proportion of heavy drinking days (HDD) (0.76% HDD less; 95% CI: 1.48 to 0.04; moderate certainty); (ii) decreasing number of drinks per drinking day (SMD = 0.54 less; 95% CI: 0.77 to 0.31; moderate certainty). Combined treatment in comparison with pharmacological interventions alone does not show difference (at the end of treatment) in: (i) return to any drinking (high certainty); (ii) return to heavy drinking (high certainty); (iii) proportion of abstinent days (high certainty).
- In adults with alcohol dependence, combined treatment compared with psychosocial/ pharmacological interventions alone does not show difference in number of people with adverse events, dropouts from treatment (moderate or high

certainty), and dropouts due to adverse events (moderate or high certainty).

- There are differences across medicines, in particular: (i) combined naltrexone plus psychosocial treatment is more effective compared with psychosocial/ pharmacological interventions alone for several outcomes at the end of treatment (moderate or high certainty); (ii) combined acamprosate plus psychosocial treatment is more effective in comparison with pharmacological interventions alone for reducing number of drinks per drinking day at the end of treatment (moderate certainty); (iii) combined acamprosate plus psychosocial treatment does not show difference in comparison with psychosocial interventions alone (moderate certainty); (iv) combined disulfiram plus psychosocial interventions do not show difference in comparison with psychosocial interventions alone (low certainty).

Remarks

- The term “combined treatment” refers to psychosocial interventions provided together with pharmacological treatment.
 - Psychosocial interventions considered included: CBT, couples therapy, psychodynamic therapy, behavioural therapies, social network therapy, contingency management, motivational interventions, 12-step facilitation and mutual help groups.
 - Pharmacological treatment considered included: acamprosate, disulfiram and naltrexone.
- The term “alcohol dependence” refers to diagnosis according to the ICD-10 or DSM-IV criteria or equivalent ICD-11 and DSM-5 diagnosis.

Research gaps

- All studies were conducted in HICs. Further research is needed to enhance understanding on use in low-resource settings.
- Most studies comparing combined treatment to psychosocial interventions were on naltrexone. Further research on acamprosate and disulfiram is required.
- Studies comparing combined treatment to pharmacological interventions were on acamprosate or naltrexone, with no studies on disulfiram. Further research on disulfiram is required.
- Most studies focused on CBT and combined behavioural interventions with fewer studies on other psychosocial interventions. Further research is needed to understand whether the balance of effects differs by type of psychosocial intervention.

Implementation considerations

- Both naltrexone and acamprosate are relatively expensive medicines compared with disulfiram, which is considerably less expensive and may be more readily accessible in low-income settings. However, medicines may not be registered and available in all countries. The decision to use acamprosate, disulfiram or naltrexone should be

made taking into consideration harms and benefits, availability and individual preference.

- Decision on the choice and implementation of psychosocial and/or pharmacological treatment should be based on individual characteristics of the person it is prescribed for. Service providers should help the person make decisions about available treatments, based on providing relevant information (e.g. possible side-effects, counterindications, costs). Even if it is not possible to provide combined interventions, individuals should be provided with either psychosocial or pharmacological treatment.
- Even though differences for adverse events were not identified, medicines for alcohol dependence treatment can have side-effects and service providers should monitor them carefully. The side-effect profile is generally acceptable for most people receiving acamprosate or naltrexone. Education of the individual and their carer (e.g. family member) regarding potential adverse events with disulfiram is important. The balance of benefits versus harms in non-specialized settings is unclear.
- Discontinuities in drug availability and access to psychosocial interventions (common in LMICs) may interfere with continuation of treatment and should be considered in planning treatment.

3.2 Anxiety (ANX)



ANX1. In adults with anxiety disorders (excluding social anxiety disorder and specific phobias), are antidepressants (tricyclic antidepressants [TCAs] and selective serotonin reuptake inhibitors [SSRIs]) effective and safe compared with treatment as usual, waitlist, no treatment, or alternative psychological or pharmacological treatments?

Recommendation (new):

Selective serotonin reuptake inhibitors (SSRIs) should be considered for adults with panic disorder. If SSRIs are not available, consider offering tricyclic antidepressants (TCAs). SSRIs should be considered for adults with generalized anxiety disorder (GAD).

Strength of recommendation: Conditional

Certainty of evidence: Low

Justification

- Evidence was included from two meta-analyses: Chawla et al., 2022 (87 RCTs on pharmacological interventions for panic disorder) (33); and Slee et al., 2019 (89 RCTs on pharmacological interventions for GAD) (34).
- Low-quality evidence suggested reduced levels of anxiety symptoms in adults with GAD and panic disorder using antidepressants (TCAs or SSRIs). Very low-quality evidence suggested reduced levels of anxiety symptoms in adults with anxiety disorders (GAD or panic disorder) using either psychological interventions or antidepressant medicines and no consistent difference between the two in direct comparisons.
- See recommendation [ANX2](#) for further detail on psychological interventions.

Remarks

- SSRIs for panic disorder examined included: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline. Individual analyses indicated sertraline and escitalopram may be the most efficacious with lowest risk of adverse effects. Fluvoxamine, paroxetine and fluoxetine indicated favourable efficacy but higher risk of adverse events. Citalopram indicated minimal efficacy and high risk of adverse events. However, individual analyses are

based on limited data and should be interpreted with caution.

- TCAs for panic disorder examined included imipramine and clomipramine.
- SSRIs for GAD examined included citalopram, escitalopram, fluoxetine, paroxetine and sertraline. Paroxetine was the only SSRI that demonstrated increased risk of adverse events (dropout) relative to placebo.
- Evidence on the use of TCAs (imipramine) for GAD was limited and indicated they did not demonstrate a significant effect relative to placebo.
- TCAs are generally less well tolerated than SSRIs and therefore are recommended for consideration in cases where SSRIs are not available for adults with panic disorder.
- Antidepressants should only be offered in those contexts where health workers are competent (e.g. qualified, trained and supervised) to prescribe psychotropic medicines.
- Psychological interventions should be offered only in contexts where individuals are competent (e.g. qualified, trained and supervised) to provide them and demonstrate necessary competencies to do so.
- In resource-constrained settings, antidepressants (SSRIs for GAD; SSRIs as first-line treatment and then TCAs as second-line treatment for panic disorder) that are accessible should be favoured, as evidence

does not indicate a statistically significant difference between the individual antidepressant medicines in these classes for anxiety disorders.

- TCAs are generally less well tolerated than SSRIs and also generally considered less safe, due to anticholinergic side-effects, toxicity, psychomotor and cognitive impairment risks, and lethality risks in cases of acute intoxication or overdose. TCAs are therefore recommended for consideration in cases where SSRIs are not available for adults with panic disorder.
- TCAs should be avoided in older adults and in people diagnosed with glaucoma, heart conditions, prostatism or other prostate conditions, or at risk of these conditions.
- Consider increased risk of bleeding associated with SSRIs, particularly for older people or people taking other medicines that can damage the gastrointestinal mucosa or interfere with clotting (e.g. non-steroidal anti-inflammatory drugs [NSAIDs]).
- Antidepressants should be offered combined with psychological treatments, when sufficient resources are available.

Research gaps

- The majority of studies were conducted in HICs. Further research is needed to enhance understanding on use in low-resource settings.
- Limited evidence on outcomes such as functioning.
- Few studies directly compared psychological interventions with pharmacological interventions, particularly for adults with GAD, including for important outcomes like symptom reduction, adverse effects, acceptability, sustained response and functioning.

Implementation considerations

- Providers should keep in mind the possible adverse effects associated with antidepressant medicines, treatment availability and individual preferences. Discontinuities in drug availability (common in

LMICs) may interfere with continuation of treatment.

- Specific types of antidepressants selected should carefully consider factors such as demographic characteristics (e.g. higher risks and side-effects that may be associated with pregnancy or older age), side-effects profiles (e.g. sexual dysfunction, sleep problems, weight gain) and availability (e.g. continuous availability, costs).
- Support the person in making a decision between antidepressants and psychological interventions (if available), based on providing relevant information (e.g. possible side-effects, costs). Before prescribing medicines, discuss treatment options and any concerns the person has about taking medicines.
- Explain rationale for prescribing and provide written and verbal information on benefits and harms, side-effects, drug interactions, the importance of taking medicines as prescribed and the likely time to improvement in symptoms.
- Regularly review the effectiveness of the medicine and side-effects with the person during the first three months of treatment and every three months afterwards. For adults who experience side-effects after starting medicine, consider closer monitoring of their symptoms, reducing the dose of the medicine or stopping the medicine gradually and offering alternative interventions.
- For adults under 30 years of age who are prescribed antidepressants:
 - Inform them of increased risk of suicidal thinking and self-harm behaviour among younger people when taking these medicines.
 - Ensure follow-up within one week after initiating the medicines if at all possible.
 - Monitor and follow-up on suicidal thinking and self-harm on regular (e.g. weekly) basis within the first month after initiating the medicine or changing the dose.
- If the medicine is effective, continue use for at least six months after remission to reduce likelihood of relapse.

ANX2. Is brief, structured psychological treatment (e.g. cognitive behavioural therapy [CBT], problem-solving therapy [PST]) better than treatment as usual in people with anxiety disorders (excluding social anxiety disorder and specific phobias)?

Recommendation (new):	Brief, structured psychological interventions based on principles of cognitive behavioural therapy (CBT) should be offered for adults with generalized anxiety disorder (GAD) and/or panic disorder
Strength of recommendation:	Strong
Certainty of evidence:	Moderate

Justification

- Evidence was extracted from four systematic reviews: Parker et al., 2021 (19 RCTs on psychological interventions for adults with anxiety disorders in non-specialized care settings) (35); Haller et al., 2021 (23 RCTs on psychological interventions for adults with anxiety disorders) (36); van Dis et al., 2020 (69 RCTs on long-term outcomes following psychological interventions for adults with anxiety disorders) (37); and Papola et al., 2020 (136 RCTs on psychological interventions for adults with panic disorder) (38).
- Moderate-certainty evidence suggests reduced levels of anxiety in adults with anxiety disorders (GAD or panic disorder) when engaging in brief, structured psychological interventions based on CBT principles. The undesirable effects were judged to be trivial.

Remarks

- Provision of psychological interventions should be based on appropriate diagnosis and need for care. Many individuals suffering transient anxiety may improve with less intensive psychosocial interventions (e.g. stress management) or basic support and problem solving.
- Face-to-face brief psychological interventions delivered by service providers is human resource-intensive as it requires substantial provider time, training and supervision.
- Integrating the provision of brief psychological interventions into primary care provides many advantages, including more holistic health care,

increased accessibility of mental health services for people in need of care, opportunities for reducing the stigma of mental health problems and reduced costs.

Research gaps

- The majority of studies were conducted in HICs. Further research is needed in LMICs.
- There were limited data on psychological interventions other than those based on principles of CBT. Further research is needed to understand if other therapies (e.g. PST) could offer similar benefit.

Implementation considerations

- Brief psychological interventions can be delivered effectively in non-specialized health-care settings as well as in other settings, including specialized mental health care and social care.
- Most psychological interventions may be delivered by a wide range of professional staff: counsellors, psychologists, nurses, lay health counsellors and health volunteers. This increases the feasibility of the implementation of psychosocial interventions.
- Task sharing has been found to be an effective approach to delivering brief psychological interventions.
- See recommendation [ANX3](#) for discussion of recommended delivery formats for brief, structured psychological interventions.
- Country adaptation and translation of training materials and tools for the provision of psychological interventions is essential.

ANX3. For adults with anxiety disorders, what is the comparative effectiveness of different formats of psychological interventions?

Recommendation (new):	<p>When brief, structured psychological interventions based on principles of cognitive behavioural therapy (CBT) are offered for adults with generalized anxiety disorder (GAD) and/or panic disorder, different delivery formats should be considered based on available resources as well as individual preferences, including:</p> <ul style="list-style-type: none"> • individual and/or group face-to-face; • digital/online and/or face-to-face; • guided and/or unguided self-help; • specialist and/or non-specialist.
Strength of recommendation:	Conditional
Certainty of evidence:	Low

Justification

- Evidence was extracted from three systematic reviews: Barkowski et al., 2020 (57 RCTs on group psychotherapy for adults with anxiety disorders) (39); Pauley et al., 2023 (47 RCTs on digital interventions for adults with anxiety disorders) (40); and Parker et al., 2021 (19 RCTs on psychological interventions for adults with anxiety disorders in non-specialized care settings) (35).
- Low-quality evidence suggests that the differences between individual versus group and digital versus face-to-face psychological interventions were small or non-existent. Additionally, while evidence does demonstrate a potential difference between guided versus unguided self-help and specialist versus non-specialist provided care, there is substantial value in expanding care through less resource-intensive means, including expanding the delivery of psychological interventions beyond care by specialists.
- In terms of undesirable effects, dropout rates were higher in group psychotherapy (RR = 1.58; 95% CI: 1.00 to 2.49).
- See [ANX2](#) for further discussion of evidence for the brief, structured psychological interventions recommended in mhGAP for GAD and/or panic disorder.
- While interventions that are provided by specialists or as guided self-help (either digitally or face-to-face) are likely to demonstrate better outcomes than those provided in groups, by non-specialists, or as unguided self-help, the latter may be suitable for adults with anxiety disorders who either (i) do not have access to face-to-face psychological treatment provided by specialists or guided self-help psychological treatment or (ii) are not willing to access such treatments.
- The choice of intervention format depends on available resources in the health system as well as individual preferences.
- Self-help psychological treatment may involve information technology (IT)-supported self-help materials and/or paper-based self-help books or visual materials and can be guided by professionals or lay workers with varying degrees of support, or can be unguided.
- Face-to-face brief psychological interventions delivered by service providers is human resource-intensive as it requires substantial provider time, training and supervision.

Remarks

- For all delivery formats listed in the recommendation, there is no inherent hierarchy or priority intended in the listing of delivery formats.

- There are concerns regarding potentially sensitive content and data privacy while using digital health interventions. Measures should be taken to ensure that digitally delivered psychological interventions are provided under conditions of safety/security, confidentiality, informed consent and privacy of data. This can include the establishment of standard operating procedures that describe protocols for ensuring consent, data protection and storage, and verifying provider licensing and credentials. Further guidance can be found in the 2019 *WHO guideline: recommendations on digital interventions for health system strengthening* (31).

Research gaps

- The majority of studies were conducted in HICs. Further research is needed to enhance understanding on use in low-resource settings.
- There is not enough data to understand the role of digital interventions for equity, equality and non-discrimination of people with anxiety disorders: while there is the potential to increase access to care, it is also possible that not all people can benefit due to the “digital divide”, which requires further research.

Implementation considerations

- Brief psychological interventions can be delivered effectively in non-specialized health-care settings, as well as in other settings including specialized mental health care and social care.
- Task sharing has been found to be an effective approach to delivering brief psychological interventions.
- Integrating the provision of brief psychological interventions into primary care provides many advantages, including more holistic health care, increased accessibility of mental health services for people in need of care, opportunities for

reducing the stigma of mental health problems and reduced costs.

- Country adaptation and translation of training materials and tools for the provision of psychological interventions is essential.
- Psychological interventions have shown to be effective for people of different ages and genders.
- If all else is equal, group face-to-face interventions are less resource-intensive per person receiving care than individual face-to-face interventions. However, groups may be more difficult to organize and require an initial individual assessment for each group member and preparation of individuals for group treatment formats. In many countries, people often do not attend for health care at pre-specified appointment times. Therefore, groups may experience high dropout rates or delayed session start times.
- Self-help books are less cost intensive but require sufficient literacy skills, which can be limited in various settings. Materials that rely on visual or audio media may be useful alternatives.
- Setting up and sustaining digital health solutions can be costly, while costs for individual users are usually not very high, making implementation feasible for the end user.
- There is a need to consider the potential digital divide across population groups with some having unequal access to and skills to use digital technologies. Access might be particularly difficult for certain population groups with poor access to network services, mobile devices or electricity, and/or with low literacy and digital literacy skills. Measures should be taken to address inequities in access to mobile devices so that further inequity is not perpetuated in accessing health information and services, including mechanisms to ensure individuals who do not have access to mobile devices can still receive appropriate services.

ANX4. Are stress management techniques better than (more effective than/as safe as) treatment as usual in adults with anxiety disorders (excluding social anxiety disorder and specific phobias)?

Recommendation (new):	Stress management techniques, namely relaxation and/or mindfulness training, should be considered for adults with generalized anxiety disorder (GAD) and/or panic disorder.	
	Strength of recommendation:	Conditional
	Certainty of evidence:	Low

Justification

- Data were extracted from a systematic review: Kim and Kim, 2018 (16 RCTs on relaxation techniques and mindfulness techniques for adults with anxiety disorders) (41).
- Low-quality evidence suggests reduced levels of anxiety symptoms in adults with anxiety disorders (GAD and panic disorder) using stress management techniques. No reviews examining undesirable effects were identified.

Remarks

- In resource-constrained settings, stress management techniques may be more feasible than psychological interventions, which may require more time and capacity-building.
- Stress management techniques may include a wide range of approaches (e.g. relaxation training, mindfulness) and should be evidence-based and selected based on individual preference and local context.
- Integrating stress management into primary care and/or other general health-care services provides many advantages, including more holistic health care, increased accessibility of mental health services for people in need of care, opportunities for reducing the stigma of mental health problems and reduced costs.

Research gaps

- No reviews examined important outcomes like adverse events, acceptability or functioning in adults with anxiety disorders following stress management.
- Few studies examined follow-up data to determine sustained impact of stress management.
- Evidence pertained to stress management techniques provided in-person. However, in resource-constrained settings, online delivery formats may be more feasible for providing these techniques. Further evidence is needed on this.

Implementation considerations

- Stress management techniques should be taught or delivered by competent providers who are qualified, trained and supervised.
- Stress management can often be provided through guided or unguided self-help formats. IT-based self-help interventions often require access to computers and/or smart phones, and sometimes the internet, which can make these interventions difficult to access for people with low-income or those living in poverty.

ANX5. Is advice on physical activity better than (more effective than/as safe as) treatment as usual, waitlist, no treatment in adults with anxiety disorders (excluding social anxiety disorders and specific phobias)?

Recommendation (new):	Structured physical exercise should be considered for adults with generalized anxiety disorder (GAD) and/or panic disorder.	
	Strength of recommendation:	Conditional
	Certainty of evidence:	Very low

Justification

- Evidence was extracted from three systematic reviews: Ramos-Sanchez et al., 2021 (13 RCTs on physical exercise for adults with anxiety disorders) (42); Vancampfort et al., 2021 (14 RCTs on physical exercise for adults with anxiety disorders) (43); and Machado et al., 2022 (8 RCTs on physical exercise for adults with panic disorder) (44).
 - Very low-quality evidence suggests reduced levels of anxiety symptoms in adults with anxiety disorders after engaging in physical exercise.
 - There is also general evidence of the direct health and mental health co-benefits of physical exercise for all adults with mental disorders.
 - In the evidence supporting this recommendation, the specific type and format of physical exercise varied. Evidence appears to indicate the effects of physical exercise on reducing anxiety symptoms in adults with GAD and/or panic disorder is not explained by exercise setting, duration or intensity. There is also no current evidence on inter-individual differences in these effects.
- activity performed during leisure time with the primary purpose of improving or maintaining physical fitness, physical performance, or health.
- It is recommended that all adults ages 18–64 (not specific to those with GAD or panic disorder) “should do at least 150–300 minutes of moderate-intensity aerobic physical activity; or at least 75–150 minutes of vigorous-intensity aerobic physical activity; or an equivalent combination of moderate- and vigorous-intensity activity throughout the week, for substantial health benefits” (45).
 - This current recommendation is specific to the additional benefits of physical exercise in the reduction of anxiety symptoms in adults with GAD or panic disorder.
 - In resource-constrained settings, physical exercise may be more feasible than more intensive psychological interventions.
 - The type of physical exercise may vary and depend on individual preferences and feasibility for the person.
 - In cases of moderate-to-severe anxiety disorders, this intervention may be most appropriate as an adjunct to pharmacological and/or psychological interventions.

Remarks

- The 2020 *WHO guidelines on physical activity and sedentary behaviour* provide further detail on physical exercise and physical activity.
 - Exercise is defined as “a subcategory of physical activity that is planned, structured, repetitive, and purposeful in the sense that the improvement or maintenance of one or more components of physical fitness is the objective.” “Exercise” and “exercise training” are frequently used interchangeably and generally refer to physical

Research gaps

- The types of physical exercise that were studied varied in reviews. Further research which includes standardized intervention formats and/or clear description of the exercise activities, duration and intensity would help to clarify best practices.

Implementation considerations

- There is cultural variability in the perceived value of physical exercise, which may lead to variability in uptake and successful implementation of this intervention in different settings.
- This intervention for the reduction of anxiety symptoms in adults with GAD or panic disorder may be less appropriate for people engaged in physical labour or otherwise with an active lifestyle and instead may be more relevant for those with less active lifestyles.

ANX6. Are benzodiazepines better than (more effective than/as safe as) placebo for adults with anxiety disorders (excluding social anxiety disorders and specific phobias)?

Recommendation (new):	Benzodiazepines are not recommended for the treatment of adults with generalized anxiety disorder (GAD) and/or panic disorder. For emergency management of acute and severe anxiety symptoms, benzodiazepines may be considered but only as a short-term (3–7 days maximum) measure.	
	Strength of recommendation:	Strong
	Certainty of evidence:	Low

Justification

- Evidence was extracted from three systematic reviews: Slee et al., 2019 (89 RCTs on pharmacological interventions for adults with GAD) (34); Breilmann et al., 2019 (24 RCTs on benzodiazepines for adults with panic disorder) (46); and Shinfuku et al., 2019 (8 RCTs on long-term outcomes for adults with anxiety disorders following benzodiazepine use) (47).
- Low-quality evidence suggests reduced levels of anxiety and improved functioning in adults with anxiety disorders but also increased risk of adverse effects and dropout following benzodiazepine use.
- A strong recommendation was made despite low-quality evidence since the GDG concluded that the risks of the intervention outweighed the benefits.

Remarks

- Benzodiazepines for panic disorder examined in the included reviews were alprazolam, adinazolam, clonazepam, diazepam and midazolam.
- Benzodiazepines for GAD examined in the included reviews were not reported individually.
- Benzodiazepines have a risk of dependence. Use beyond the recommended 3- to 7-day maximum

period requires monitoring and follow-up by trained specialist providers and is beyond the scope of this guideline.

Research gaps

- The majority of studies were conducted in HICs. Further research is needed to enhance understanding on use in low-resource settings.
- There is a limited number of studies on the long-term effectiveness and safety of benzodiazepines. Further research would help to quantify the risks of longer term use.

Implementation considerations

- Benzodiazepines should not be universally prescribed to treat anxiety or distress and should instead be used in select cases of acute and severe anxiety or distress and where other treatment approaches have proved ineffective or unavailable.
- Before prescribing benzodiazepines, discuss the treatment options and any concerns the person has. Explain the rationale for prescribing this medicine and provide written and verbal information on benefits and harms; side-effects; drug interactions; the importance of taking medicines as prescribed;

risks when driving, operating machinery, etc.; the likely time to improvement in symptoms; and the potential for addiction.

- Discontinue benzodiazepines gradually as soon as symptoms improve to avoid tolerance.
- For adults who demonstrate potential signs of dependence, consider management approaches

for benzodiazepine withdrawal and dependence; for further information, see the 2015 *Update of the Mental Health Gap Action Programme (mhGAP) guidelines for mental, neurological and substance use disorders* (7) and the 2016 *mhGAP intervention guide* module on “Disorders due to substance use” (9).

ANX7. Is collaborative care better than (more effective than/as safe as) treatment as usual, waitlist, no treatment for adults with depression or anxiety (living with chronic health conditions)?

Recommendation (new):	Collaborative care should be considered for adults with depression and/or anxiety and physical health conditions.	
	Strength of recommendation:	Conditional
	Certainty of evidence:	Low

Justification

- Evidence was extracted from three systematic reviews: Xiao et al., 2021 (89 RCTs on pharmacological interventions for adults with GAD) (48); Stein et al., 2020 (24 RCTs on benzodiazepines for adults with panic disorder) (49); and van der Feltz-Cornelis et al., 2021 (8 RCTs on long-term outcomes for adults with anxiety disorders following benzodiazepine use) (50).
- Low-certainty evidence suggests reduced levels of depression and anxiety and improved physical health outcomes in adults with chronic health conditions who receive collaborative care (CC) services. The GDG also identified additional evidence that was included as additional information in the evidence profile, which suggested reduced levels of anxiety in adults with physical health conditions.

Remarks

- The CC model generally adds one new team member to the medical team (a care manager) and includes coordinated consultation with mental health care providers. It typically involves:
 - a health-care team sharing tasks, with a care manager (a new role) coordinating care;

- approaches to identifying people in need of support (through use of systematic screening or case identification);
- implementation of evidence-based interventions (where psychological interventions can be delivered by the care manager or, where available, by a non-specialist counsellor);
- administration of medicine, if indicated (by a general medical care provider);
- monitoring of mental health symptoms by recording results of measurement tools in a basic registry that is regularly reviewed by the case manager to inform changes to care; and
- a mental health care provider, who consults with the team and supervises the care manager and general medical care provider.
- Care managers often also facilitate access to community resources where indicated (e.g. housing or employment services).
- Physical health conditions concern both communicable and noncommunicable diseases.
- Conditionality in this recommendation is based solely on availability of resources. In settings where resources are available, CC should be implemented.

- Integrating mental health services into primary care settings and physical disease programmes through the CC model is an effective way of increasing access to mental health care, improving health outcomes and reducing stigma towards people with mental health conditions, particularly for populations where prevalence of mental disorders (e.g. depression) may be high.
- There is wide variation in how CC has been implemented as CC is a model of providing care, rather than an intervention in and of itself. Nonetheless, this model of care can be resource intensive, though it is feasible in LMIC settings when necessary resources are allocated.
- CC should only be implemented in settings where there are human resources allocated to support the intervention.
- Specific efforts are required to identify, orient and build capacity in medical teams, care providers and mental health care providers for this model of integrated care.
- Acceptability of CC can be increased when implementors:
 - engage key stakeholders (e.g. service-users, providers, policy-makers, and community members) in the development of the CC model to ensure it will be suitable for the setting in which it is being implemented;
 - incorporate trusted community members in the CC team;
 - adapt CC training materials, guidelines, and interventions to be culturally appropriate; and
 - address lack of understanding of integrated care, understanding of mental health and confidence in delivering mental health care, resistance due to feeling overburdened, stigma or medical hierarchies among providers.

Research gaps

- Further research is needed to demonstrate feasibility and effectiveness of CC when adapted to LMICs.

Implementation considerations

- CC is generally more intensive in terms of human resources than usual care models (although there is evidence to suggest it may provide good economic value). The human resources required for CC vary widely based on how the components of the model are adapted for implementation in a given setting.

3.3 Child and adolescent mental disorders (CAMH)



CAMH1. What is the effectiveness and safety of pharmacological interventions for children with a diagnosis of attention deficit hyperactivity disorder (ADHD)?

Recommendation (update):	<p>For children 6 years old and above and adolescents who have an attention deficit hyperactivity disorder (ADHD) diagnosis, methylphenidate may be considered, provided that:</p> <ul style="list-style-type: none"> • ADHD symptoms are still causing persistent significant impairment in at least one domain of functioning (education, interpersonal relationships, occupation), after the implementation of environmental modifications in schools, at home or in other relevant settings; • a careful assessment of the child/adolescent has been conducted; • the child/adolescent and the caregivers, as appropriate, have been informed about ADHD treatment options and supported in decision-making; • methylphenidate prescription is made by, or in consultation with, a specialist. 				
	<table> <tr> <td>Strength of recommendation:</td><td>Conditional</td></tr> <tr> <td>Certainty of evidence:</td><td>Low</td></tr> </table>	Strength of recommendation:	Conditional	Certainty of evidence:	Low
Strength of recommendation:	Conditional				
Certainty of evidence:	Low				

Justification

- Data were extracted from a systematic review: Cortese et al., 2018 (133 RCTs; 81 in children and adolescents, 51 in adults, and 1 in both) (51).
- Methylphenidate treatment shows substantial effects on symptom reduction when compared with placebo and has lower certainty of evidence for less substantial effects on school functioning in children 6 years and older and adolescents.
- Methylphenidate prescription should be issued by, or in consultation with, a specialist, as substantial weight loss is reported in children and adolescents on methylphenidate treatment.
- There is limited evidence on efficacy and tolerability beyond 12 weeks and on treatment satisfaction.
- There are increasing concerns related to overmedicalization and overtreatment of ADHD in children.

Remarks

- Methylphenidate treatment should be offered only in the context of a management plan that address psychosocial risks and vulnerabilities and environmental factors that have an impact on symptoms, functioning, well-being and participation of children and adolescents with ADHD.
- Methylphenidate treatment should be combined when possible with brief parent behavioural therapies.
- Children and adolescents receiving methylphenidate should be maintained under close clinical monitoring for improvement in symptoms and prevention of adverse effects.
- A specialist care provider trained on management of ADHD should reassess the child/adolescent's management plan for ADHD at least once per year.
- The rationale for specialist assessment before prescription of methylphenidate is that diagnosis of ADHD requires specialist clinical judgement especially given the risks of misuse of methylphenidate.

Research gaps

- There is a need for strengthened intervention designs that include long-term follow-up to ascertain lasting intervention effects, including adverse effects and acceptability in children and adolescents. It is critically important that more evidence is made available on protocol adherence, misuse/safety and treatment satisfaction when treatment with methylphenidate is prescribed and monitored in primary health care settings.

Implementation considerations

- It is important to consider the health system’s capacity to enforce and implement protocols for ADHD diagnosis; to prescribe and initiate methylphenidate treatment by or in close consultation with a specialist; and to ensure careful clinical monitoring for side-effects, clinical response, adherence, treatment acceptability, and dose adjustment.

CAMH2. What is the effectiveness of psychosocial interventions for promotion of mental health and prevention of mental health conditions in children?

Recommendation (new):	2.1 Universally delivered psychosocial interventions that use curriculum-based, family-based, exercise-based methods and/or social and personal skills development to improve emotional regulation should be considered for promotion of psychosocial well-being in children.	
	Strength of recommendation:	Conditional
	Certainty of evidence:	Very low

Justification

- Evidence was extracted from three systematic reviews: Pandey et al., 2018 (49 studies; 17 cluster randomized trials and 32 RCTs) (52); Caldwell et al., 2021 (79 studies; 43 cluster randomized studies and 34 RCTs) (53); and Smith et al., 2021 (8 RCTs) (54).
- For universal interventions, moderate desirable effects were reported for psychosocial well-being (SMD = 0.4; 95% CI: 0.31 to 0.48). No significant undesirable effects were reported in the reviews included. There was some evidence on acceptability from Caldwell et al. (2021); eight studies in this review reported on acceptability of the intervention in universal primary settings, with generally positive findings (53).
- Despite some promising findings, the majority of outcomes were associated with very low certainty of evidence. This certainty of evidence may be related to smaller observed effects in universal samples, high author ratings of risk of bias due to self-report

outcomes (common in these types of interventions), or relatively small numbers of child participants contributing to these data overall.

- School-based interventions appear to be a promising entry point for delivering promotive and preventive interventions at scale, with additional costing details needed.

Remarks

- Emotional regulation is a psychological construct which entails the capacity to control one’s emotions, the ability to have positive interactions with others, the capacity to avoid inappropriate or aggressive actions, and the ability to carry out self-directed learning (52). As such, it is a critical domain underpinning broader psychosocial well-being.
- Universally-delivered interventions designed to improve psychosocial well-being (emotional regulation) utilized a combination of approaches: curriculum-based, family-based, exercise-based

methods and/or social and personal skills development – all of which were found to perform equally well.

- In addition, a classroom-based behaviour management intervention was effective in reducing aggressive, disruptive and oppositional behaviours.
- It is unknown whether any type of psychosocial interventions improve emotional problems. No reviews reported on prevention of mental health diagnoses (depression, anxiety, conduct disorder, self-harm or stigma).

Research gaps

- Despite a substantial body of evidence on reducing emotional problems for all children ages 5–10, there is a need for strengthened intervention designs for this age group that are evaluated using rigorous study designs, and that include long-term follow-up data to ascertain lasting intervention effects.
- For aggressive, disruptive and oppositional behaviours, studies should measure behaviours outside the classroom.

- Cost-effectiveness studies of interventions conducted with this age group are also limited. This was beyond the scope of the systematic reviews conducted for this update.
- There is a clear need to develop, implement and evaluate interventions for all children ages 5–10 with a broader set of outcomes, including mental health diagnoses, self-harm and mental health stigma.

Implementation considerations

- These interventions have been largely implemented in school-based settings, by teachers or other school staff, and sometimes involving parents or siblings.
- Efforts should be made to reach out-of-school children and children exposed to vulnerabilities, including children with disabilities.
- It is important to assess and address psychosocial risks and environmental determinants affecting the mental health of children.

Recommendation (new):

2.2 Psychosocial interventions that include cognitive behavioural therapy (CBT), psychoeducation and family-focused treatment approaches should be offered to children whose parents have mental health conditions for the prevention of depression and anxiety.

Strength of recommendation: Strong

Certainty of evidence: Low

Justification

- Evidence was extracted from one systematic review: Lannes et al., 2021 (20 RCTs) (55).
- For targeted interventions, small desirable effects were reported for emotional problems at post-intervention (SMD = -0.25; 95% CI: -0.37 to -0.14) and short-term follow-up (SMD = -0.2; 95% CI: -0.37 to -0.03), as well as for depression/anxiety diagnoses (RR = 0.53; 95% CI: 0.34 to 0.84).
- Despite the low/very low overall certainty of evidence for most outcomes, for the critical outcome

of depression and anxiety (diagnosis) for children ages 5–10, the evidence was of moderate quality. Hence, a strong recommendation is proposed.

- Most studies had higher risk of bias linked to self-report measures, as is common with this type of intervention. The studies' results were relatively consistent, and the significant findings outweigh potential harms. This review also included heterogeneous types of interventions addressing child mental health in the context of a range of parental mental health conditions.

Remarks

- Interventions that reduced incidence of depression and anxiety in children included those with CBT and psychoeducational aspects. Often these were family-focused interventions, with therapeutic components tailored to the parent’s mental health condition. Booster sessions may be an important part of longer-term impacts of the interventions.
- These interventions can be helpful in preventing emotional problems in the short-term. It is not known whether they improve psychosocial well-being, reduce emotional problems in the immediate or long-term, or reduce aggressive, disruptive or oppositional behaviours. No studies reported on diagnoses of conduct dissocial disorder, self-harm or stigma.

Research gaps

- More evidence on novel recruitment and retention approaches, including digital and multicomponent interventions, could support better outcomes with this specific group of children and parents.

- Long-term follow-up studies are required to understand mental health and illness trajectories in this group of children.
- No studies reported on diagnoses of conduct dissocial disorder, self-harm or stigma. Further research is required on these aspects.

Implementation considerations

- There may be stigma associated with these targeted interventions. Engaging families with a severe mental illness may be experienced as intrusive, and communicating about children’s risk for developing mental health conditions may be stigmatizing or shameful for families and further impact caregivers’ well-being. Efforts to provide sensitive engagement, with emphasis on strengths-based support and promotive aspects, is of paramount importance.
- There is also a large evidence base on parenting programmes, which provide a useful entry point for targeted family-focused interventions.

CAMH3. What is the effectiveness of psychosocial interventions (apart from caregiver skills training) to improve development, well-being, functioning and school participation in children and adolescents with neurodevelopmental delays and disabilities?

Recommendation (new):	3.1 Psychosocial interventions focused on social skills training and developmental behavioural approaches should be offered to improve development, well-being and functioning in children and adolescents with autism.	
	Strength of recommendation:	Strong
	Certainty of evidence:	Low

Justification

- Evidence was extracted from three meta-analyses: Wang et al., 2021 (51 RCTs) (56); Soares et al., 2021 (18 RCTs) (57); and Wolstencroft et al., 2018 (10 RCTs) (58).
- The evidence indicated large clinically and statistically significant effects. Weighted mean effect sizes from meta-analytic syntheses include:

d = 0.57 (95% CI: 0.24 to 0.90) for social-emotional skills (child development), d = 0.40 (95% CI: 0.24 to 0.56) for reduction in anxiety (children’s health and well-being), and d = 0.55 (95% CI: -0.03 to 1.1.3) for reduction in problem behaviour (functioning).

- The certainty of the evidence was often downgraded because studies were subject to the risk of bias due to difficulty in blinding the interventions and due to

reliance on self-reported outcomes, both of which are common in these types of intervention studies. However, a strong recommendation was made despite the low certainty of evidence thanks to the relative consistency of the study results and the fact that significant benefits substantially outweighed potential harms.

Remarks

- Social skills training involves instruction on appropriate and expected social behaviours in everyday situations. These interventions can be delivered in multiple formats including peer-mediated interventions and social skills groups. Social skills training can also be delivered in didactic or individual formats, in which case opportunities for practice with peers must be provided.

Research gaps

- While medium-to-large effects have been shown in extant studies, greater deficits, relative to typical populations, remain for social skills in individuals with autism.
- Research examining most significant factors or intervention components will help ensure treatments provide the most benefits.
- Many social skills treatment studies have focused on individuals with higher-functioning autism; less is known about social skills treatments for other individuals with autism.
- Lack of research specific to females with autism has been noted. Given differences in social development

and interests between males and females, additional research on social skills treatments for females is warranted.

Implementation considerations

- Adjustments to treatments in order to meet the needs of children and adolescents with autism may be needed. These may include greater use of written and visual information, more concrete and structured cognitive approaches, providing for short breaks and involvement of a carer in treatment sessions.
- These approaches should be implemented in the context of broader strategies focused on promoting inclusive and enabling environments for all, including children and young people with autism.
- Make reasonable adjustments or adaptations and provide visual supports if useful.
- Ensure that all children and adolescents with autism have full access to health- and social-care services, including mental health services.
- Promote access to information about treatment options suitable for the child or adolescent's needs and developmental level, and promote supported decision-making.
- Make arrangements to support children and adolescents with autism and their family and carers during times of increased need and transitions, such as puberty and starting or changing schools.

Recommendation (new):	3.2 Cognitive behavioural therapy (CBT) should be offered to children and adolescents with autism with anxiety.	
	Strength of recommendation:	Strong
	Certainty of evidence:	Moderate

Justification

- Evidence was extracted from one meta-analysis: Sharma et al., 2021 (19 RCTs) (59).
- Large significant effects were evident ($d = 0.40$; 95% CI: 0.24 to 0.56) for reduction in anxiety (children's health and well-being) (59).
- Findings similar for children under 10 years old (12 studies; $d = 0.40$; 95% CI: 0.02 to 0.79) and children and adolescents aged 10 years and older (11 studies; $d = 0.76$; 95% CI: 0.22 to 1.30; Wang et al., 2021) (56).

Remarks

- For young people who have the verbal and cognitive ability to engage in CBT, CBT provides an opportunity to reflect on thoughts and feeling that contribute to anxiety symptoms and to learn the skills to challenge dysfunctional beliefs and replace them with more positive thinking.

Research gaps

- Comparisons between CBT format and specific CBT programmes are not well studied.
- Most extant studies on CBT for autism involve individuals with higher-functioning autism; effects of intervention are less well known for individuals with more severe limitations in functioning.

Implementation considerations

- Adjustments to treatments in order to meet the needs of children and young people with autism may be needed. These may include greater use of written and visual information, more concrete and structured cognitive approaches, providing for short breaks and involvement of a carer in treatment sessions.
- These approaches should be implemented in the context of broader strategies focused on promoting inclusive and enabling environments for all, including children and young people with autism.
- Make reasonable adjustments or adaptations and provide visual supports if useful.
- Ensure that all children and young people with autism have full access to health- and social-care services, including mental health services.
- Promote access to information about treatment options suitable for the child or adolescent's needs and developmental level, and promote supported decision-making.
- Make arrangements to support children and adolescents with autism and their family and carers during times of increased need and transitions, such as puberty and starting or changing schools.

Recommendation (new):	3.3 Psychosocial interventions focused on social skills, cognitive and organizational skills training should be considered to improve development and functioning in children and adolescents with attention deficit hyperactivity disorder (ADHD).	
	Strength of recommendation:	Conditional (social skills training, cognitive interventions) and Strong (organizational skills training)
	Certainty of evidence:	Moderate

Justification

- Evidence was extracted from three meta analyses: Storebø et al., 2019 (25 RCTs) (60); Cortese et al., 2015 (16 RCTs) (61); and Bikic et al., 2017 (12 RCTs) (62).
- There were statistically significant findings showing medium to large effects across the three meta-analyses: $d = 0.09$ (95% CI: -0.09 to 0.27) to $d = 0.56$ (95% CI: 0.38 to 0.74) for functional outcomes, including increased attention, decreased problem behaviour and better school performance.

Remarks

- Social skills training interventions tend to focus on problem-solving, control of emotions, and verbal and non-verbal communication. Social skills training consists of role play, exercises and games, as well as homework. Social skills training is taught in groups and is a relatively short intervention typically lasting between 8 and 12 weeks. The duration of each group session is usually 50–90 minutes.
- Organizational skills training focuses on organization of materials, time and tasks and includes a variety of learning activities, such as teaching, modelling and feedback to build new skills or improve performance of existing skills.
- Cognitive interventions focus on improving cognitive processes through controlled exposures to information processing tasks.

Research gaps

- Extant research studies have involved multiple outcome assessment methods and tools; examination of more standard measures of functional skills will be helpful in future research.

- Comparison between intervention methods will provide useful information on the most effective intervention components (these comparisons may be done in primary studies and then using advanced synthesis methods and models).
- Examination of the most effective treatment types matched to participant characteristics (e.g. age, ADHD symptom presentation/severity) is also needed.

Implementation considerations

- Both individual and group-based formats can be considered, adjusted to the needs of the children and young people. These may include greater use of written and visual information, more concrete and structured cognitive approaches, providing for short breaks and involvement of a carer in treatment sessions.
- These approaches should be implemented in the context of broader strategies focused on promoting inclusive and enabling environments for all, including children and adolescents with ADHD.
- Make reasonable adjustments or adaptations and provide visual supports if useful.
- Ensure that children and youth with ADHD have full access to health- and social-care services, including mental health services.
- Promote access to information about treatment options suitable for the child or young person's needs and developmental level, and promote supported decision-making.
- Make arrangements to support children and young people and their family and carers during times of increased need and transitions, such as puberty and starting or changing schools.

Recommendation (new):	3.4 Beginning-to-read interventions should be offered to improve communication and academic performance in children with disorders of intellectual development.	
	Strength of recommendation:	Strong
	Certainty of evidence:	Moderate

Justification

- Evidence was extracted one systematic review and meta-analysis: Reichow et al., 2019 (7 RCTs) (63).
- A small but statistically significant effect was found for language skills (3 studies, 222 participants), as measured by standardized norm-referenced language assessments ($d = 0.28$; 95% CI: 0.03 to 0.54).

Remarks

- Beginning-to-read interventions include elements of phonological awareness, letter-sound instruction and decoding.
- Evidence supports delivery of beginning-to-read intervention in school settings by specialists (special education teachers/researchers) and non-specialists (teacher assistants). Beginning-to-read interventions varied in intensity but used common instructional strategies based on social learning theories and behavioural technologies.

Research gaps

- Studies did not include individuals with disorders of intellectual development who were dual language learners. This is an area in need of further research.

Implementation considerations

- Intervention sessions occurred in school settings. Research supports delivery of beginning-to-read intervention in school settings by specialists (special education teachers/researchers) and non-specialists (teacher assistants).
- Ensure that all children and young people with disorders of intellectual development have full access to health- and social-care services, including mental health services.
- Promote access to information about treatment options suitable for the child's needs and developmental level, and promote supported decision-making.
- Make arrangements to support children with disorders of intellectual development and their family and carers during times of increased need and transitions, such as puberty and starting or changing schools.

Recommendation (new):

3.5 Early communication interventions involving direct instruction approaches should be considered for improving expressive phonological skills and reducing stuttering for children with developmental speech disorders.

Strength of recommendation: Conditional

Certainty of evidence: Very low

Justification

- Evidence was extracted from two systematic reviews: Rinaldi et al., 2021 (26 RCTs, 1 systematic review) (64); and Brignell et al., 2021 (8 RCTs) (65).
- There is evidence that interventions aimed at expressive phonological skills produce appreciable results (64). Evidence on the effect of intervention on receptive phonological skills is too limited to draw any conclusion. There is limited evidence that targeted interventions on expressive vocabulary acquisition are effective. No studies were identified that investigated the effectiveness of receptive vocabulary interventions in children with developmental language disorder (DLD). There is some evidence that interventions aimed at morphological and syntactic expressive skills in children with DLD are effective. The mean age of participants in the studies included in the review was 2.5–7.4 years (overall mean age could not be calculated because not all studies reported mean age of participants).
- One review considered stuttering (65). This review showed significant effects of the communication intervention, including follow-up (weighted MD 3.79 more; 95% CI: 0.27 to 7.32) in children who stutter. The ages of the participants in the studies included in the review ranged from 3 to 6 years.

Remarks

- For children who stutter, the direct instruction approach involved speech-language therapists working with parents to deliver a behaviour

modification programme with a strong reinforcement contingency component. Both studies included in the meta-analysis by Brignell et al. (2021) included data at follow-up time points that showed treatment gains had been maintained, suggesting lasting effects of treatment (65).

- For improving expressive phonological skills in children with developmental speech disorders, the intervention approach involved expressive phonological tasks, phonological awareness, and auditory discrimination and listening activities.

Research gaps

- There was little evidence on communication interventions for older children, thus a gap exists in this area.
- Additional meta-analyses of RCTs for speech disorders would also expand knowledge of effective interventions in this area.

Implementation considerations

- The location of intervention sessions can vary from structured settings (e.g. school, typically used in early treatment) to less structured naturalistic settings (e.g. home, used later in treatment).
- Treatment of school-age and older children may require modifications to ensure the treatment is developmentally appropriate.
- The available evidence involved instruction from speech and language therapists in high-resource settings; implications for adaptations in lower-resource settings may be needed.

Recommendation (new):	3.6 Psychosocial interventions using cognitive learning techniques to enhance communication and social competencies should be considered for children and adolescents with neurodevelopmental disabilities.	
	Strength of recommendation:	Conditional
	Certainty of evidence:	Low

Justification

- Evidence was extracted from one meta-analysis: Ahn and Hwang, 2018 (6 RCTs) (66).
- Despite a promising finding ($d = 0.64$; 95% CI: 0.40 to 0.87) for adaptive behaviour (functioning), the primary finding had a low certainty of evidence (66).
- This certainty of evidence was related to the small number of studies included in the meta-analytic synthesis (six studies) with small sample sizes, concerns with blinding of outcome assessors, and heterogeneity. Results of the review are consistent with other meta-analyses and primary studies in this area.

Remarks

- Everyday functioning is a target of many interventions for individuals with neurodevelopmental disabilities and is thus a critical domain to examine. It refers to the ways in which individuals function in everyday aspects of life and includes communication skills, socialization and daily living skills.
- Cognitive interventions are a heterogeneous group of treatments to stimulate and optimize cognitive processes, such as working memory, attention, executive functions, communication and social competences, often in a simultaneous and broad manner via computerized and adaptive cognitive exercises. They can be adapted to the child's cognitive profile.

- Cognitive interventions can be delivered as components of broader comprehensive interventions targeting adaptive and life skills.
- Child participants included in the review by Ahn and Hwang (2018) were younger children; in five of six studies, children were under the age of 7 at the beginning of treatment.

Research gaps

- The review by Ahn and Hwang (2018) was the only systematic review taking a transdiagnostic approach that could be identified. More efforts are needed to synthesize evidence on interventions to optimize outcomes in children and young people with neurodevelopmental disabilities taking a functional approach.

Implementation considerations

- These interventions have been largely implemented in home- and clinic-based settings, by clinicians and trained specialists.
- Caregivers are often involved in treatment, either as participants or as individuals trained to deliver the intervention strategies in the absence of the primary intervention agent.

Recommendation (new):

3.7 Structured physical exercise should be considered to improve development, including social and communication development, and functioning in children and adolescents with autism.

Strength of recommendation: Conditional

Certainty of evidence: Low

Justification

- Evidence was extracted from one meta-analysis: Huang et al., 2020 (12 RCTs) (67).
- The analysis showed large effects favouring treatment for functional outcomes (reduction in autism symptoms; $d = 1.14$; 95% CI: 0.25 to 2.02) and one developmental outcome (social skills; $d = 0.58$; 95% CI: 0.29 to 0.87) and a medium effect for communication skills (child development; $d = 0.29$; 95% CI: 0.04 to 0.55) (67).
- Quality of evidence was downgraded due to the small number of studies included in the meta-analysis that mapped to the population of interest (4 studies).

Remarks

- Structured physical exercise included planned or purposeful sports games, aerobic exercise, cycling and yoga. This could be completed individually or in pairs or groups.
- The *WHO guidelines on physical activity and sedentary behaviour* advises that children and adolescents should do at least an average of 60 minutes per day of moderate- to vigorous-intensity, mostly aerobic, physical activity across the week (68). Vigorous-intensity aerobic activities, as well as those that strengthen muscle and bone, should be incorporated at least three days a week.
- These approaches should be implemented in the context of broader strategies focused on promoting inclusive and enabling environments for all, including children and adolescents with autism.

Research gaps

- Limited evidence was available from LMICs.
- Evidence was not identified on young adults (age > 18).

- More research is needed on digital and virtual reality-based exercise programmes, particularly tailored low-cost app-based programmes for promotion of physical exercise in the young adult population.
- Research on low-intensity physical activity (e.g. movement breaks) would also help in understanding the extent to which these programmes confer benefit.

Implementation considerations

- Structured physical exercise programmes will be available in a variety of settings including educational, rehabilitation, recreation and other community settings.
- Adjustments to structured physical exercise programmes in order to meet the needs of children and adolescents with autism may be needed. These may include greater use of written and visual information, more concrete and structured approaches, providing for short breaks and involvement of a carer in treatment sessions.
- Make reasonable adjustments or adaptations and provide visual supports if useful.
- Ensure that all children and adolescents with autism have full access to health- and social-care services, including mental health services.
- Promote access to information about treatment options suitable for the child or adolescent's needs and developmental level, and promote supported decision-making.
- Make arrangements to support children and adolescents and their family and carers during times of increased need and transitions, such as puberty and starting or changing schools.

Recommendation (new):	3.8 Structured physical exercise should be considered to improve motor skills and functioning, including attention and executive functioning, and reduce anxiety and problem behaviours in children and adolescents with attention deficit hyperactivity disorder (ADHD).	
	Strength of recommendation:	Conditional
	Certainty of evidence:	Very low

Justification

- Evidence was extracted from two meta-analyses: Sun et al., 2022 (15 RCTs) (69); and Cerrillo-Urbina et al., 2015 (8 RCTs) (70).
- There were large effects favouring treatment for developmental outcomes (motor skills; $d = 0.67$; 95% CI: 0.22 to 1.12), health and well-being (anxiety; $d = 0.66$; 95% CI: 0.13 to 1.18) and functional outcomes (attention and executive functioning; $d = 0.60$; 95% CI: 0.11 to 1.10; and $d = 1.22$; 95% CI: 0.61 to 1.82), respectively). Medium effect were found for problem behaviour ($d = 0.24$; 95% CI: 0.21 to 0.69).
- Certainty of evidence was very low for all outcomes.

Remarks

- Structured physical exercise included planned or purposeful sports games, aerobic exercise, cycling and yoga. These suggested activities reflect those reported in the literature. However, the examples can be adapted to reflect those most relevant to the local content, e.g. cycling or yoga may not be common activities in all settings.
- This could be completed individually or in pairs or groups.

Research gaps

- Evidence was not identified in older adolescents or young adults (age > 14).
- Interventions were 6–12 weeks in duration. The longer-term effects of structured physical exercise are unknown.

- More research is needed on digital- and virtual reality-based exercise programmes, particularly tailored low-cost app-based programmes for promotion of physical exercise in this population.
- Research on low-intensity physical activity (e.g. movement breaks) would also help in understanding the extent to which these programmes confer benefit.

Implementation considerations

- Both individual and group-based formats can be considered, adjusted to the needs of the children and adolescents. These may include greater use of written and visual information, more concrete and structured approaches, providing for short breaks and involvement of a carer in treatment sessions.
- These approaches should be implemented in the context of broader strategies focused on promoting inclusive and enabling environments for all, including children and young people with ADHD.
- Make reasonable adjustments or adaptations and provide visual supports if useful.
- Ensure that children and adolescents with ADHD have full access to health- and social-care services, including mental health services.
- Promote access to information about treatment options suitable for the child or adolescents' needs and developmental level, and promote supported decision-making.
- Make arrangements to support children and adolescents and their family and carers during times of increased need and transitions, such as puberty and starting or changing schools.

Recommendation (new):	3.9 Specialized instructional techniques should be considered to improve academic performance, including writing skills, reading comprehension and maths, in children and adolescents with developmental learning disorders.	
	Strength of recommendation:	Conditional
	Certainty of evidence:	Very low

Justification

- Evidence was extracted from two meta-analyses: Ciullo et al., 2020 (42 studies; 24 RCTs and 18 other group comparative designs) (71); and Jitendra et al., 2018 (19 experimental and quasi-experimental studies) (72).
- There was a large effect favouring specialized instructional techniques for functioning in academic performance for writing skills ($d = 0.63$; 95% CI: 0.00 to 1.26) and medium effects favouring treatment for functioning in academic performance for reading comprehension ($d = 0.33$; 95% CI: 0.23 to 0.86) and mathematics ($d = 0.37$; 95% CI: 0.18 to 0.56).
- Quality of evidence was downgraded due to inclusion of non-randomized studies in meta-analyses.

Remarks

- Participants in the primary studies included in the meta-analyses had a range of developmental learning disorders including impairment in reading, impairment in written expression and impairment in mathematics.
- Participants in the included studies were children and adolescents who were attending primary or secondary schools (i.e. 5- to 18-year-olds).

- In the studies included in the meta-analyses, specialized instruction included many supplemental instructional techniques including increased material structure and visual models, alternative or digital texts, peer-assisted learning strategies and other additional/supplemental materials.

Research gaps

- Limited evidence was available from LMICs.
- Evidence focused only on school settings and not on adolescents in occupational settings. Further research is needed on adolescents not in education.

Implementation considerations

- Intervention sessions occurred in non-specialist school settings. Research supports delivery of specialized instruction in school settings by specialists (special education teachers/researchers) and possibly non-specialists (teacher assistants) under the supervision of specialists.
- Instructional techniques can be used to modify the existing curriculum or provide an alternative curriculum where appropriate.
- These approaches should be implemented in the context of broader strategies focused on promoting inclusive and enabling environments for all, including children and young people with developmental learning disorders.

Recommendation (new):	3.10 Task-oriented instruction should be considered to improve motor skills and task performance in children with developmental coordination disorders.	
	Strength of recommendation:	Conditional
	Certainty of evidence:	Very low

Justification

- Evidence was extracted from one meta-analysis: Miyahara et al., 2017 (8 RCTs, 7 quasi-RCTs) (73).
- There was a significant effect favouring treatment for development (motor skills; MD = 3.63; 95% CI: 1.39 to 5.88). Descriptive analyses suggested improvements in occupational and task performance for some outcomes in two trials included in the meta-analysis.
- The quality of evidence was downgraded due to the small number of studies included in the meta-analysis that mapped to the population of interest (6 studies).

Remarks

- Participants in the studies included in the meta-analysis were children 5–12 years old.
- Task-oriented instruction was defined by Miyahara et al. as an intervention that was described as task-oriented and a formally required practice of a specific task or occupation, including task-specific training, cognitive motor approaches, ecological

intervention, neuromotor task training and cognitive orientation to daily occupational performance.

- These approaches should be implemented in the context of broader strategies focused on promoting inclusive and enabling environments for all, including children and young people with development coordination disorders.

Research gaps

- Evidence was not available from older adolescents or young adults (age > 12).
- The longer-term effects of task-oriented instruction are unknown.
- More high-quality evidence is required as the identified evidence included non-randomized studies.

Implementation considerations

- Interventions are likely to need a specialist provider.
- Interventions should be adapted to mimic the students' learning environments as closely as possible.

Recommendation (new):	3.11 Structured physical exercise and activity should be offered to improve development outcomes, including motor skills and functioning, in children and adolescents with cerebral palsy.	
	Strength of recommendation:	Strong
	Certainty of evidence:	Low

Justification

- Evidence was extracted from one meta-analysis: Liang et al., 2021 (27 RCTs) (74).
- There were large effects favouring treatment for developmental outcomes (fine motor skills; $d = 0.75$; 95% CI: 0.02 to 1.51) and functional outcomes (SMD range 0.76 to 1.00). Smaller but statistically significant effects were also shown for gross motor skills (development; $d = 0.15$; 95% CI: 0.09 to 0.40) and gait speed and muscle strength (functioning; MD = 0.05; 95% CI: 0.00 to 0.10; and MD = 0.92; 95% CI: 0.19 to 1.64, respectively).

Remarks

- Physical exercise using both traditional and digital or virtual formats were shown to be effective for children and adolescents with cerebral palsy.
- Physical exercise or activity included sports games, aerobic exercise, cycling and yoga. The physical exercise or activity could be completed individually or in pairs or groups.
- Physical exercise or activity completed using digital or virtual reality included activity done while playing video games.
- These approaches should be implemented in the context of broader strategies focused on promoting inclusive and enabling environments for all, including children and adolescents with cerebral palsy.

Research gaps

- Limited evidence was available from LMICs.
- More research is needed to assess the benefits of tailored low-cost app-based programmes for promotion of physical exercise in this population.

- Research on low intensity physical activity (e.g. movement breaks) would also help in understanding the extent to which these programmes confer benefit in developmental outcomes.

Implementation considerations

- Structured physical exercise programmes will be available in a variety of settings including educational, rehabilitation, recreation and other community settings.
- Make adjustments to structured physical exercise programmes in order to meet the needs of children and adolescents with cerebral palsy where appropriate. The programme should be adapted to ensure that the physical exercise demands and format match the individual child or adolescent's needs and preferences.
- Take into account negative impacts of environmental barriers, including programme providers' attitudes and physical barriers.
- Ensure that all children and adolescents with cerebral palsy have full access to health- and social-care services, including mental health services.
- Promote access to information about treatment options suitable for the child or adolescent's needs and developmental level, and promote supported decision-making.
- Make arrangements to support children and adolescents and their family and carers during times of increased need and transitions, such as puberty and starting or changing schools.
- The technology required for digital or virtual reality programmes in the identified studies is not yet available on a mobile device. A specific gaming device is currently required for this activity.

CAMH4. In children and adolescents with emotional disorders, what is the effectiveness and safety of using pharmacological interventions?

Recommendation (new):	4.1 Pharmacological interventions are not recommended in children and adolescents with anxiety disorders.	
	Strength of recommendation:	Strong
	Certainty of evidence:	Low

Justification

- Evidence was extracted from one meta-analysis: Dobson et al., 2019 (22 RCTs) (75).
- Benefits and potential harms need to be considered in the context of low certainty of evidence, to take into account capacities to correctly identify children and adolescents with anxiety who may benefit from pharmacological treatments and to monitor adverse effects and risk of suicidality in non-specialist settings.
- There is very low certainty of evidence supporting benefits of SSRIs, as a group, in improving anxiety symptoms and there is moderate-quality evidence supporting treatment response to group SSRI. The available evidence shows no significant difference between both all TCAs (pooled) and benzodiazepines compared with pill placebo in improving anxiety symptoms.
- Group SSRIs and benzodiazepines had significantly more discontinuations due to adverse effects than pill placebo. Treatment-emergent suicidality was significantly greater in paroxetine-treated children and adolescents compared with those receiving placebo, and significantly lower in sertraline-treated children and adolescents compared with those receiving placebo. The available evidence points to the fact that there is a lack of reliable data on suicidality for many pharmacological treatments for

emotional disorders in children, and care providers should closely monitor suicide risk when children and adolescents take any antidepressant medicines.

- Since the harms of the intervention outweigh the benefits, a strong recommendation is made against use of pharmacological interventions for children and adolescents with anxiety disorders.

Remarks

- Diagnosis of anxiety in children can be influenced by the cultural context and requires a comprehensive assessment of determinants at a family level and in the environment to reduce risks of overmedicalization.

Research gaps

- Additional evidence is required to establish the benefits and safety of prescribing pharmacological treatment for anxiety in children and adolescents in non-specialist settings.
- Almost all evidence refers to HICs. Further research is needed in LMICs.

Implementation considerations

- Access to psychotherapy, particularly cognitive behavioural interventions and caregiver skills training, in line with other mhGAP recommendations, remains important for children with anxiety disorders and their caregivers.

Recommendation (new):	4.2 Antidepressant medicines are not recommended for the treatment of children 12 years of age and below with depressive episode/disorder.	
	Strength of recommendation:	Strong
	Certainty of evidence:	Low

Justification

- Evidence was extracted from two meta-analyses: Hetrick et al., 2021 (26 RCTs) (76); and Zhou et al., 2020 (71 RCTs) (77).
- The available evidence on pharmacological interventions for depression in children under 12 is very limited.
- SSRI use is associated with an increased risk of suicide and suicide attempts (78). Since the harms of the intervention outweigh the benefits, a strong recommendation is made against use of antidepressants for treatment of depression in children 12 years of age or younger.

Remarks

- Diagnosis of depression in children can be influenced by the cultural context and requires a

comprehensive assessment of determinants at a family level and in the environment to reduce risks of overmedicalization.

Research gaps

- Additional evidence on the use of pharmacological interventions in children is required, with due attention to monitoring adverse effects and risk of overmedicalization.

Implementation considerations

- Access to psychotherapy, particularly cognitive behavioural interventions and caregiver skills training, in line with other mhGAP recommendations, remains important for children with moderate-to-severe depression and their caregivers.

Recommendation (new):	4.3 If psychosocial interventions alone prove ineffective in adolescents (13–17 years) with moderate-to-severe depression, referral to or consultation with a specialist should be offered, to undertake a more comprehensive assessment and to explore initiation of fluoxetine in combination with psychological treatments.	
	Strength of recommendation:	Strong
	Certainty of evidence:	Low

Justification

- Evidence was extracted from two meta-analyses: Hetrick et al., 2021 (26 RCTs) (76); and Zhou et al., 2020 (71 RCTs) (77).
- The available very low-certainty evidence shows that SSRIs (pooled together) and fluoxetine alone are related to statistically significant improvements in depressive symptoms in adolescents with moderate-to-severe depression. However, none of the antidepressants were significantly better than treatment as usual (TAU) in improving

depressive symptoms and the positive effects of antidepressants are considered to be small and not clinically significant when compared with placebo (76).

- SSRI use is associated with an increased risk of suicide and suicide attempts (78). It remains critical to ensure close monitoring of treatment effects and suicide-related outcomes (combined suicidal ideation and suicide attempt) in adolescents treated with SSRIs.

Remarks

- The effects of antidepressants might vary between individuals, so the adolescents, their carers and clinicians should carefully balance the risk–benefit profile of efficacy, acceptability and suicide risk in young people with depression on a case-by-case basis.
- It is important to inform adolescents and carers, as appropriate, about treatment options and jointly reassess treatment goals and management plans on a regular basis.

Research gaps

- The available evidence on the effects of antidepressants in adolescents is of very low certainty and almost entirely from HICs. Adolescents considered at risk of suicide are frequently excluded from trials, so one cannot be confident about the effects of these medicines for these individuals. There is no evidence on reduction in risky behaviours and user/family satisfaction.
- If an antidepressant is being considered for an individual, this should be done in consultation with the adolescent and their family/caregivers, given findings that some of these medicines may be associated with increased risk of suicide and suicide attempts.
- The cost of these medicines is high, with the exception of fluoxetine, which is also on the WHO

EML (13). There must be available and competent human resources to prescribe medicines safely and monitor any adverse effects.

Implementation considerations

- Access to psychotherapy, particularly CBT, in line with other mhGAP recommendations, remains important for adolescents with moderate-to-severe depression.
- In case psychosocial interventions alone prove ineffective, the adolescent and the caregiver, as appropriate, should be referred to a specialist for careful consideration of benefits and risks associated with initiation of fluoxetine, possibly in combination with psychological treatment, in close consultation with the adolescent and family, as appropriate.
- Fluoxetine treatment should be offered only in the context of a management plan that addresses psychosocial risks and vulnerabilities and environmental factors that have an impact on depression symptoms and functioning.
- Adolescents receiving fluoxetine should be maintained under close clinical monitoring for improvement in symptoms and prevention of adverse effects.
- A specialist care provider should reassess the adolescent's management plan at least once per year.

3.4 Conditions related to stress (STR)



STR1. For adults with post-traumatic stress disorder (PTSD), are psychological interventions effective compared with treatment as usual, waitlist or no treatment?

Recommendation (update):	<p>Psychological interventions should be considered for adults with post-traumatic stress disorder (PTSD). Namely, these include:</p> <ul style="list-style-type: none"> • individual face-to-face cognitive behavioural therapy (CBT) with a trauma focus;⁶ • group face-to-face CBT with a trauma focus; • digital/remote CBT with a trauma focus; • eye movement desensitization and reprocessing (EMDR); • stress management.
Strength of recommendation:	Conditional
Certainty of evidence:	Low

Justification

- The evidence review team updated an existing systematic review and meta-analysis: Phelps et al., 2022 (101 RCTs examining the effectiveness of psychological treatments in adults with PTSD) (82).
- Low-quality evidence suggests there may be no difference between face-to-face CBT with a trauma focus and digital CBT with a trauma focus, between CBT with a trauma focus and EMDR, and between CBT with a trauma focus and stress management. Meanwhile, individual CBT with a trauma focus is likely to demonstrate better outcomes than group CBT with a trauma focus, and EMDR is likely to demonstrate better outcomes than stress management. However, the less effective interventions may still be suitable for adults with PTSD who either (i) do not have access to more effective treatment or (ii) are not willing to access such treatments.

Remarks

- The choice of intervention format largely depends on available resources in the health system as well as individual preferences.
- Although studies show that group CBT with a trauma focus and EMDR are more effective than stress management, in resource-constrained settings, the latter may be the more feasible option.

Research gaps

- Few studies were conducted in context of the LMICs, limiting the generalizability of these recommendations.
- Future meta-analyses comparing psychological interventions for adults with PTSD may benefit from NMA approaches in order to provide stronger evidence on comparisons.

⁶ The term cognitive behavioural therapy (CBT) with a trauma focus is synonymous with the term trauma-focused CBT (TF-CBT), as used in the United Kingdom's National Collaborating Centre for Mental Health guidance (79) and in Cochrane reviews (e.g. Bisson and Andrew 2005 [80]). It is noted that in the traumatic stress literature the latter term also has a more narrow definition for a very specific and widely disseminated multicomponent CBT protocol for children and adolescents developed by Cohen et al., 2000 (81).

Implementation considerations

- Brief psychological interventions can be delivered effectively in non-specialized health-care settings, as well as in other settings including specialized mental health care facilities and in the context of social care.
- Face-to-face brief psychological interventions delivered by service providers are human resource-intensive because they require substantial provider time, training and supervision.
- Task sharing has been found to be an effective approach to delivering brief psychological interventions. However, CBT with a trauma focus and EMDR can include complex techniques. The clinician using these techniques should also have received training in their provision and demonstrated competencies to provide them. The provider should have additional capacities to support the person receiving treatment, including (i) the ability to make differential diagnosis, (ii) problem-solving techniques and (iii) relaxation/stabilizing techniques. Given the delicate and technical nature of EMDR, implementation by lay providers may carry risks. Lay providers should be comprehensively trained and closely supervised when providing any intervention for people experiencing conditions related to stress, including PTSD.
- Integrating the provision of brief psychological interventions into primary care provides many advantages, including more holistic health care, increased accessibility of mental health services for people in need of care, opportunities for reducing the stigma of mental health problems and reduced costs.
- Country adaptation and translation of training materials and tools for the provision of psychological interventions is essential.
- Psychological interventions have shown to be effective for people of different ages and genders.
- If all else is equal, group face-to-face interventions are less resource-intensive per person receiving care than individual face-to-face interventions. However, groups may be more difficult to organize and require an initial individual assessment for each group member and preparation of individuals for group treatment formats.
- Stress management can often be provided through guided or unguided self-help formats. IT-based self-help interventions often require access to computers and/or smart phones, and sometimes the internet, which can make these interventions difficult to access for low-income individuals or those living in poverty.
- Self-help books are less cost intensive but require sufficient literacy skills, which can be limited in various settings. Materials that rely on visual or audio media may be useful alternatives.

STR2. For children and adolescents with PTSD, are psychological interventions effective compared with treatment as usual, waiting list or no treatment?

Recommendation (update):	<p>Psychological interventions should be offered for children and adolescents with post-traumatic stress disorder (PTSD). Namely, these include:</p> <ul style="list-style-type: none"> • individual face-to-face cognitive behavioural therapy (CBT) with a trauma focus; • group face-to-face CBT with a trauma focus; • eye movement desensitization and reprocessing (EMDR).
Strength of recommendation:	Strong
Certainty of evidence:	Moderate

Justification

- The evidence review team updated an existing systematic review: Phelps et al., 2022 (45 RCTs examining the effectiveness of psychological treatments in children and adolescents with PTSD) (82).
- Moderate-quality evidence suggests reduced rates of PTSD symptoms in children and adolescents using these interventions. While EMDR demonstrated better outcomes than CBT with a trauma focus in research trials, both are effective and the latter may be suitable for children and adolescents with PTSD who do not have access to EMDR.

Remarks

- Given the delicate and technical nature of EMDR, implementation by lay providers may carry risks. Lay providers should be comprehensively trained and closely supervised when providing any intervention for people experiencing conditions related to stress, including PTSD.

Research gaps

- Few studies were conducted in context of the LMICs, limiting the generalizability of these recommendations.
- Future meta-analyses comparing psychological interventions for children and adolescents with PTSD may benefit from NMA approaches in order to provide stronger evidence on comparisons.

Implementation considerations

- Brief psychological interventions can be delivered effectively in non-specialized health-care settings, as well as in other settings including specialized mental health care and social care or in education settings for children and adolescents.
- Face-to-face brief psychological interventions delivered by service providers are human resource-intensive because they require substantial provider time, training and supervision.
- Task sharing has been found to be an effective approach to delivering brief psychological interventions. However, CBT with a trauma focus and EMDR can include complex techniques. The clinician using these techniques should also have received training in their provision and demonstrated competencies to provide them. Also, the provider should have additional capacities to support the person receiving treatment, including (i) the ability to make differential diagnosis, (ii) problem-solving techniques and (iii) relaxation/stabilizing techniques.
- Integrating the provision of brief psychological interventions into primary care provides many advantages, including more holistic health care, increased accessibility of mental health services for people in need of care, opportunities for reducing the stigma of mental health problems and reduced costs.

- Country adaptation and translation of training materials and tools for the provision of psychological interventions is essential.
- Psychological interventions have shown to be effective for people of different ages and genders.
- If all else is equal, group face-to-face interventions are less resource-intensive per person receiving care than individual face-to-face interventions. However, groups may be more difficult to organize and require an initial individual assessment for each group member and preparation of individuals for group treatment formats.
- Stress management can often be provided through guided or unguided self-help formats. IT-based self-help interventions often require access to computers and/or smart phones, and sometimes the internet, which can make these interventions difficult to access for low-income individuals or those living in poverty.
- Self-help books are less cost intensive but require sufficient literacy skills, which can be limited in various settings. Materials that rely on visual or audio media may be useful alternatives.

3.5 Dementia (DEM)



DEM1. For carers of people with dementia, are psychosocial interventions effective in improving their outcomes?

Recommendation (update):	1.1 Psychosocial interventions – namely mindfulness-based interventions, multicomponent interventions, psychoeducation and psychotherapy/ counselling – should be offered for carers of people living with dementia.	
	Strength of recommendation:	Strong
	Certainty of evidence:	Low
	1.2 Respite care should be considered for carers of people living with dementia.	
	Strength of recommendation:	Conditional
	Certainty of evidence:	Low
	1.3 Depression and anxiety in carers of people living with dementia should be assessed and treated in line with mhGAP recommendations for depression and anxiety.	
	Strength of recommendation:	Strong
	Certainty of evidence:	Low

Justification

- Data were extracted from six systematic reviews: Cheng et al., 2020 (83); González-Fraile et al., 2021 (84); Lee et al., 2020 (85); Lee et al., 2020 (86); Walter and Pinquart, 2020 (87); Xu et al., 2020 (88).
- The extracted data pertained to 10 interventions: (i) psychoeducation; (ii) counselling and psychotherapy (including CBT); (iii) mindfulness-based interventions and complementary and alternative medicine (CAM); (iv) support groups, emotional support, social support; (v) care coordination and case management; (vi) training of the care-recipient with carer involvement; (vii) multicomponent interventions; (viii) remotely delivered interventions; (ix) behavioural activation; and (x) respite care.
- Psychosocial interventions to help carers produce small effects, favouring interventions with on average low to very low certainty of evidence.
- The most robust evidence exists for multicomponent interventions that may produce moderate positive effects on carer ability, knowledge, skills and mastery and small effects on carer burden and stress, subjective well-being, health-related quality of life and social support.
- Psychoeducation in combination with cognitive-behavioural techniques, mindfulness-based interventions, psychotherapy or counselling may also produce a wide range of positive carer effects of small to large magnitude including reduced carer depressive symptoms, carer burden and stress, and anxiety; as well as increased subjective well-being and health-related quality of life.
- Globally, family members and close friends provide most of the care and support for people living with dementia, with caregiving hours accounting for 50% of the global cost of dementia care (15). Informal caregiving is associated with significantly

poorer mental health outcomes for carers compared with the general population (89), with depression and anxiety being particularly common. For these reasons, and given that the benefits exceed the harms, a strong recommendation has been made despite low certainty of evidence.

- Evidence for utilizing respite care (i.e. temporary relief from caregiving duties through the provision of substitute care in the form of in-home care, day care, or temporary admission of the person with dementia to a care facility) (87) to improve carer outcomes is of critically low quality and certainty, producing small beneficial effects on depressive symptoms and carer burden/stress. Regardless, encouraging carers to take regular breaks from their caregiving responsibilities should be considered an important element in supporting carers of people with dementia.

Remarks

- For the purpose of this guideline, carers of people with dementia are family members, close friends and other informal carers. Carers may live together with the person with dementia or in separate households. Individual circumstances of the carer and the person with dementia need to be considered in the planning and provision of support to affected families.
- The term “psychosocial intervention” is used loosely in research. Interventions are rarely manualized and often do not fall into mutually exclusive categories. Brief descriptions for recommended interventions are provided below (in alphabetical order).
 - “Mindfulness-based interventions” here is used as an umbrella term for mindfulness, meditation and yoga techniques as well as mindfulness-based cognitive therapy and mindfulness-based stress reduction (83).
 - “Multicomponent interventions” refer to interventions that use multiple approaches, such as counselling, support groups and respite, included in the same programme but without any one being the dominating component (83).
 - “Psychoeducation” refers to educational programmes with psychological or psychotherapeutic components that provide standardized information and focus on increasing carers’ knowledge of dementia and developing

specific coping skills to deal with caregiving challenges; may be delivered individually or in group-settings if the therapeutic components are adapted for delivery in a structured psychoeducational format (83).

- “Psychotherapy/counselling” as defined by Cheng et al., 2020 (83) refers to interventions that involve implementation of specified forms of individual or group therapy or counselling, typically behaviour therapy, cognitive therapy, conventional CBT but also newer theoretical orientations such as acceptance-commitment therapy. They are distinguished from psychoeducational programmes in that they are usually delivered by professional psychologists or therapists and place stronger emphasis on the development and utilization of the therapeutic relationship as part of the treatment process.
- A range of other interventions have been considered as part of this update. No specific recommendations have been made as reported effects were domain-specific, with overall low to very low certainty of evidence.
 - Training of the person with dementia (in which the carer participated) may be effective in increasing carer ability, knowledge, skills or mastery and reducing depressive symptoms in carers with low to very low certainty.
 - Remotely delivered interventions may have a small advantage over information-only control interventions but produce slightly greater drop-out rates.
- There was insufficient evidence to recommend support groups and/or care coordination/case management as psychosocial interventions for carers of people living with dementia (83,86). However, these aspects may be included or combined with other interventions as may be the case with multicomponent interventions (see above).
- Importantly, providing carers with interventions and support (e.g. carer education, carer skills training, social support, case management and multicomponent interventions) may also reduce symptoms in people living with dementia (90,91).
- It is important for health workers to be aware of the high prevalence of depression and anxiety in

carers of people with dementia (89) and assess and manage accordingly.

- In view of lacking systematic/meta-analytic evidence on cost-effectiveness of carer interventions, primary research studies suggest that carer interventions may be cost-effective, not incurring higher health-care utilization costs than treatment as usual (TAU) (92). Of note, carer support interventions are often peer-led and provided by civil society, therefore implemented outside the health system, yet contributing hugely to the care and support of affected families.

Research gaps

- Most evidence on carer interventions originated from HICs, providing limited insights as to how effective and feasible interventions may be in low-resource settings. Similarly, there is a lack of data on the needs and effectiveness of interventions for carers belonging to ethnic minorities or otherwise marginalized groups. However, systematic evidence published after the census date for this update suggests interventions recommended here may also be effective for specific cultural subgroups such as Hispanic carers (93).
- While the evidence for dementia carer interventions has increased considerably over the last two decades, it remains limited. Generally, reported effect sizes are very small. Existing research design limitations hamper the ability to demonstrate statistically and clinically meaningful effects of interventions. This pertains, for example, to a lack of sensitive and value-based outcome measures, the impracticality of blinding research participants to which intervention they are receiving, and difficulties with recruitment and retention of carers in trials. Underreporting of confounding variables such as service utilization and concomitant medicine use in carers for comorbid conditions such as depression or anxiety further limit the ability to isolate intervention from other effects. Future research should investigate effects of carer interventions to otherwise treatment-naïve carers and try to establish dose effects for carer interventions.
- There were no studies identified in the reviews that compared individual interventions with each other and the optimal intervention duration is not known. Instead, interventions often include

multiple components or combine approaches, which hampers the ability to identify active or most effective ingredients. These aspects require further attention.

- No systematic review evaluated the cost-effectiveness of interventions. Existing studies usually evaluate single activities (e.g. peer support groups, art activities) and/or investigate the cost-effectiveness of group support for people with dementia and their carers without necessarily disaggregating cost benefits/return on investment for each beneficiary group.

Implementation considerations

- *Lack of available services:* A recent systematic review suggests that despite much research being undertaken in the area of carer interventions, implementation readiness remains low and existing work has not been delivered in terms of accessible solutions to care (94). This results in often lacking support services for dementia carers, especially in LMICs and rural or remote areas (95,96).
- *Barriers and enablers of service delivery:* Carer interventions are largely deemed feasible to implement and likely most effective when provided in groups (97). However, according to a scoping review by Bayly et al. (2020), common barriers to service utilization include: low awareness of available services, cost of service, transportation challenges, need for respite, difficulty getting the person with dementia to services, values and beliefs (e.g. reluctance to reach out for help, belief that family should provide care), stigma around dementia and the use of support services, service not meeting a need/incompatible (98). In addition, carers report limited time as a major barrier for accessing training and support (99).
- *Consider individual circumstances and setting:* Individual factors and circumstances such as gender, relationship to and cohabiting with the person with dementia, and whether caregiving responsibilities are shared with others can affect depression and anxiety symptoms and their likelihood of seeking help and accessing services.
- *Need for cultural adaptation:* Based on a systematic review by Akarsu et al. (2019), basic levels of cultural adaptation of carer interventions (e.g. only translating generic materials or having bilingual and bicultural staff) appear less effective than

interventions that are developed with the target ethnic minority or cultural group's preferred method of engagement in mind (100).

- *Costs of interventions:* According to Hu et al., 2021, the costs and effects of interventions supporting informal carers of people with dementia might be affected by the inclusion of different intervention components, specific carer characteristics, and the follow-up periods considered (101).
- *Modes of delivery of interventions:* Different delivery modes of carer interventions, including digital or remotely delivered interventions have been reported to be effective. For example: CBT delivered via internet, telephone or individual sessions were equally effective in reducing depressive symptoms in carers (102); multicomponent carer

eHealth interventions delivered via the internet, telephone and combined technologies generally produced positive (albeit varying) effects regarding depression, anxiety, caregiver burden, stress, self-efficacy, knowledge and skill improvements (103). Additionally, carers of people with dementia found internet-based interventions mostly to be effective, efficient, and satisfactory (104). App-based mobile interventions for dementia carers resulted in positive effects on carer competency (SMD = 0.434; 95% CI: 0.093 to 0.775), and quality of life (SMD = 0.794; 95% CI: 0.310 to 1.278), while other outcomes were non-significant: caregiver burden (SMD = -0.315; 95% CI: -0.681 to 0.052), depression (SMD = -0.236; 95% CI: -0.517 to 0.046) and stress (SMD = -0.295; 95% CI: -0.708 to 0.118) (105).

DEM2. For people with dementia and comorbid depression, do psychological interventions (including cognitive behavioural therapy, behavioural activation therapy, interpersonal therapy and counselling) produce any benefit and/or harm compared with controls?

Recommendation:

There was insufficient evidence to update the recommendation, so the existing recommendation remains valid.

Psychological interventions – namely cognitive behavioural therapy (CBT), interpersonal therapy (IPT), structured counselling and behavioural activation therapy (BAT) – should be considered for people living with dementia and mild-to-moderate depression.

Strength of recommendation: Conditional

Certainty of evidence: Low

Justification

- There is limited low-quality evidence based on a Cochrane Review by Orgeta et al. (2014) that the use of psychological treatments may reduce symptoms of depression in this population (106).
- The evidence review team carried out further searches of systematic reviews published between 2015 and 2018 and new primary research (limited

to RCTs and controlled trials) published since 2015. None of the studies from the additional searches met the PICO criteria for this question. Due to this lack of new evidence, the 2014 review by Orgeta et al. was still considered the best and most up-to-date evidence on this topic. Therefore, the existing (2015) recommendation is retained and is not updated at this time.

Remarks

- Depression is common among people with dementia and is associated with significant adverse effects, including decrease in quality of life, increased need for institutionalization, greater health care utilization, higher mortality rates and increased caregiver burden.
- Psychological interventions may not be feasible as a treatment for people with severe dementia and symptoms of depression due to impaired cognitive function. An assessment by a suitably qualified health worker is the most appropriate means of judging the most appropriate treatment choice.
- For treatment of severe depression in people living with dementia, also refer to the existing mhGAP recommendation, which was validated by the GDG for this update. It reads as follows: “In people with dementia and severe depression, or when psychosocial interventions prove ineffective, the use of selective serotonin reuptake inhibitors (SSRIs) (but not tricyclic antidepressants [TCAs]) should be considered. In people with dementia and mild-to-moderate depression, antidepressants should not be offered as a first-line treatment” (7).
- The type of psychosocial intervention offered should be based upon the capacity of the health or care worker, family member or carer and individual preferences.

Research gaps

- No new systematic or primary evidence was available to assess the effectiveness of psychological interventions for people with dementia who have comorbid clinical depression for this update. This is likely a reflection of existing research design limitations rather than a lack of evidence for these interventions (e.g. specifically focusing on psychological interventions or therapies, rather than non-pharmacological interventions more broadly) in this specific sub-population (e.g. people with dementia and comorbid depression, rather than individuals with depressive symptoms).
- Instead, recent study designs and systematic reviews tend to evaluate the effectiveness of psychosocial interventions more broadly, such as cognitive,

psychological and environmental interventions on treating depression and/or depressive symptoms. The evidence for those has been considered under the new PICO question for DEM3.

- None of the primary studies available on psychological interventions were carried out in LMICs.

Implementation considerations

- Psychological therapies may be preferred to antidepressant medicine, which has been shown to lack efficacy. High levels of treatment adherence were reported in most of the trials included in the 2014 Cochrane Review.
- Presented evidence in the 2014 Cochrane Review is based on trials that included people living with mild-to-moderate dementia (106). The ability of people living with more severe dementia to access and participate in these therapies depends not only on their mental capacity but also other comorbidities and their social context. The assessment by a suitably qualified health worker is therefore paramount in judging the most appropriate treatment choice.
- Delivery of these interventions requires adequate training and supervision of a non-specialist health worker.
- Additional tailoring of psychological interventions to the specific needs of people with dementia may be required based on the setting and dementia severity. For non-pharmacological interventions for depressive symptoms more broadly experienced by people with dementia (at all stages of disease), refer to the new PICO DEM3. A recent meta-analysis on the effectiveness of psychological interventions for depression in general (i.e. not specific to dementia or any other comorbid condition) across different age groups suggests that there are no differences in effect sizes for these interventions for older adults (55–75 years), and older old adults (75 years and older) (107). Moreover, meta-analytic evidence suggests the effectiveness of such interventions for people with other neurological conditions such as Parkinson’s disease and multiple sclerosis (108).

DEM3. For people with dementia, are non-pharmacological interventions effective in improving their outcomes?

Recommendation (update):	3.1 Physical activity interventions – namely physical exercise delivered 3–4 times per week for 30–45 minutes for more than 12 weeks – should be offered to people living with dementia.	
	Strength of recommendation:	Strong
	Certainty of evidence:	High
	3.2 Non-pharmacological interventions – namely CBT, cognitive stimulation therapy and cognitive training (in alphabetical order) – should be considered for people living with dementia.	
	Strength of recommendation:	Conditional
	Certainty of evidence:	Low

Justification

- Evidence was extracted from 15 systematic reviews: Bahar-Fuchs et al., 2019 (109); Brims and Oliver, 2019 (110); Cafferata et al., 2021 (111); Kim et al., 2019 (112); Kim and Lee, 2019 (113); Lai et al., 2019 (114); Lin et al., 2021 (115); Lu et al., 2020 (116); Möhler et al., 2020 (117); Moreno-Morales et al., 2020 (118); Nagaoka et al., 2021 (119); Orgeta et al., 2022 (120); Saragih et al., 2022 (121); Wang et al., 2022 (122); and Zhou et al., 2022 (123).
- Overall, non-pharmacological interventions for people living with dementia produce small-to-large effects for critical outcomes, favouring interventions with the certainty of evidence ranging from very low to high. Most robust evidence exists for physical activity, with physical exercise interventions showing small positive effects on cognitive function and medium effects on everyday function with a high level of certainty. This was especially true for physical exercise delivered 3–4 times per week for 30–45 minutes for more than 12 weeks.
- In addition, the following non-pharmacological interventions produce positive effects on cognitive

function and depressive symptoms as well as everyday function, quality of life and overall dementia rating/severity with small to large magnitude and overall low to moderate certainty.

- Cognitive behavioural therapy (CBT) showed slightly positive effects on depression remission and negligible effects on reduction of depressive symptoms, as well as small effects on everyday function and quality of life (of moderate to low certainty, respectively).
- Cognitive stimulation therapy produces small to large effects on overall cognition and memory function with low certainty, as well as medium effects on overall dementia severity ratings with moderate certainty.
- Cognitive training produces small to large effects on individual cognitive domains, with effects potentially retained for up to 12 months with very low to moderate certainty, as well as medium effects on overall disease progression with moderate certainty.

Remarks

- The term “non-pharmacological intervention” is used to describe a wide range of cognitive, psychological/psychosocial and environmental interventions that are not necessarily mutually exclusive categories (i.e. interventions may fall into or incorporate aspects of multiple categories). Brief descriptions for all recommended interventions (in alphabetical order) are provided below.
 - “Cognitive behavioural therapy (CBT)” is an umbrella term covering a wide range of psychological approaches that aim to improve affective function. CBT focuses on the process of thought rather than content to help people accept their thoughts.
 - “Cognitive stimulation therapy” is a non-pharmacological intervention often involving group activities and social interaction used to treat cognitive decline in people with dementia. It encompasses a variety of approaches including reality orientation, validation, and/or reminiscence. Cognitive stimulation aims to improve global cognition and maintain function by stimulating multiple cognitive functions simultaneously, typically with group activities emphasizing social interaction. This approach is different from cognitive training, which targets isolated cognitive functions (e.g. memory) with individual, repetitive practice of standardized cognitive tasks.
 - “Cognitive training” is an umbrella term referring to a group of non-pharmacological interventions in which a range of techniques are applied to engage thinking and cognition with various degrees of breadth and specificity. The goals include improving or maintaining cognitive processes or addressing the impact of impairment in cognitive processes on associated functional ability in daily life.
 - “Physical activity” here refers to aerobic (cardiovascular conditioning) and anaerobic (strength training) exercises. In the *WHO guidelines on risk reduction of cognitive decline and dementia*, physical activity is also recommended for adults with normal cognition to reduce their risk of cognitive decline and may be recommended for adults with mild cognitive impairment to reduce the risk of further cognitive decline (124). The *WHO guidelines on physical activity and sedentary behaviour* recommend that all adults ages 18–64 (not specific to those with dementia) “should do at least 150–300 minutes of moderate-intensity aerobic physical activity; or at least 75–150 minutes of vigorous-intensity aerobic physical activity; or an equivalent combination of moderate- and vigorous-intensity activity throughout the week, for substantial health benefits” (68).
- A range of other non-pharmacological interventions and activities may be effective in managing individual symptoms of people with dementia but due to the low level of evidence and/or limited effectiveness on individual outcomes no specific recommendation has been made for their use. These interventions include the following (in alphabetical order).
 - Animal-assisted therapy showed a medium beneficial effect on reducing depressive symptoms with a low level of certainty.
 - Aromatherapy (lavender or melissa) may reduce agitation to a variable extent, especially for individuals with severe dementia, when used for shorter periods (i.e. 4 weeks or less) and applied through methods other than massage. The overall level of certainty was low, with the exception of use of melissa, which had moderate level of certainty.
 - Assistive technology may reduce the risk of falls in people with dementia with low level of certainty.
 - Dance-based interventions and music therapy may reduce depressive symptoms slightly with a very low to moderate level of certainty. Music therapy may also improve cognitive function slightly, with a very low level of certainty.
 - Horticultural therapy may be beneficial for treating/managing agitation in people with dementia with a moderate level of certainty.
 - Mindfulness-based interventions showed large positive effects on cognition and everyday functions with a very low level of certainty based on a single trial.
 - Multimodal interventions including art therapy showed very small effects on reducing depressive symptoms with a very low certainty.

- Personally-tailored activities may slightly reduce overall behaviours and psychological symptoms associated with dementia with a low level of certainty.
- Reminiscence therapy showed medium-to-large positive effects on depressive symptoms irrespective of dementia severity, but especially in people under the age of 80 and when delivered in group settings with very low to low levels of certainty.
- In line with current human rights standards and WHO's *Towards a dementia-inclusive society* – a toolkit for dementia-friendly initiatives (125) – it is important to promote inclusion and participation of people living with dementia in all activities, hobbies, pastimes, community events/gatherings based on the person's preferences to foster social functioning and well-being.

Research gaps

- Most research into non-pharmacological interventions is conducted in HICs and often restricted to institutional settings (i.e. long-term care facilities or other formal care settings such as day care centres), with less evidence generated for community-dwelling people with dementia as well as members of ethnic minorities and other marginalized groups. Future research should be inclusive of these populations and explore potential differential intervention effects.
- Methodological issues such as heterogeneity of non-pharmacological interventions with often unknown or multiple active ingredients, the lack of standardization for many non-pharmacological

interventions as well as small sample sizes limit the ability to determine the effectiveness of interventions and/or pool data across studies. In addition, due to the nature of certain interventions, blinding for RCTs is difficult and confounders are not necessarily reported (i.e. whether or not participants are treatment-naïve or receiving other concomitant treatment/medicine).

- No recent systematic evidence summarizing the cost-effectiveness or return on investment for these non-pharmacological interventions has been identified during searches. However, limited evidence from narrative reviews and primary research studies investigating individual non-pharmacological interventions suggests their cost-effectiveness, e.g. Burley et al., 2020 (126); Knapp et al., 2006 (127); D'Amico et al., 2015 (128).

Implementation considerations

- Tailor any intervention to the individual needs and preferences of the person living with dementia and their family/carers. Review regularly and adjust for dementia severity and decline over time.
- Tailor any intervention/support offered to individuals to their needs and abilities at the time, present choices and review/reassess at regular intervals to reduce the likelihood of interventions causing unintentional harm/adverse effects (e.g. through frustration, overload). Also consider the needs and preferences of carers.
- Costs associated with delivering individual non-pharmacological interventions will vary substantially by the type of intervention, but overall seem feasible in low-resource settings.

3.6 Depression (DEP)



DEP1. Are antidepressants (tricyclic antidepressants [TCAs] and selective serotonin reuptake inhibitors [SSRIs]) better than (more effective than/as safe as) pill placebo/treatment as usual in adults with depressive episode/disorder?

Recommendation (update):	In adults with moderate-to-severe depression, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine or sertraline (SSRIs) or amitriptyline (TCA) should be considered.
Strength of recommendation:	Conditional
Certainty of evidence:	Very low

Justification

- Evidence was extracted from two meta-analyses: Cao et al., 2021 (42 RCTs) (129) and Cipriani et al., 2018 (522 RCTs) (130).
- SSRIs (namely citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) and TCAs (namely amitriptyline) were significantly better than pill placebo in reducing depressive symptoms.
- The certainties of evidence for change in depressive symptoms, response, all-cause dropout, and dropout due to adverse events were low for citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline (all SSRIs) and for amitriptyline (TCA).
- Amitriptyline and fluoxetine are included in the WHO EML, with other SSRIs listed as alternatives (13).

Remarks

- The term “depression” refers to moderate to severe depressive episode or disorder.
- There were no studies identified in the review that included comparisons by severity of depression (e.g. moderate versus severe). However, there was no evidence of an association between baseline severity and the network estimates in meta-regression analysis.
- TCAs are generally less well tolerated than SSRIs and are also generally considered less safe, due to anticholinergic side-effects, toxicity, psychomotor and cognitive impairment risks, and lethality risks in cases of acute intoxication or overdose. TCAs are therefore recommended for consideration in

cases where SSRIs are not available for adults with panic disorder.

- TCAs should be avoided in older adults and in people diagnosed with glaucoma, heart conditions, prostatism or other prostate conditions, or at risk of these conditions.
- Consider increased risk of bleeding associated with SSRIs, particularly for older people or people taking other medicines that can damage the gastrointestinal mucosa or interfere with clotting (e.g. NSAIDs).

Research gaps

- Most of the evidence is from HICs. Further research is needed in LMICs.
- There was no direct evidence to evaluate the risk of suicide-related adverse effects of antidepressants.

Implementation considerations

- Service providers should only consider antidepressant medicine alone for adults with depression when psychological interventions are not available.
- Service providers should assess psychosocial stressors (e.g. domestic abuse, unemployment) associated with depression and include appropriate psychosocial interventions in their treatment plan.
- Providers should keep in mind the possible adverse effects associated with antidepressants, the ability to deliver either intervention (in terms of expertise and/or treatment availability) and individual preferences. Discontinuities in drug availability

(common in LMICs) may interfere with continuation of treatment.

- Generic TCAs and many generic SSRIs are associated with low acquisition costs. Cost of daily dose of generic antidepressants varies from region to region throughout the world ranging between 3% and 9% of minimum wage (131).
- For the treatment of depressive disorder, the WHO EML (13) includes:
 - TCA: amitriptyline;
 - SSRI: fluoxetine (therapeutic alternatives: citalopram, escitalopram, fluvoxamine, paroxetine and sertraline).
- The *Interagency health kit 2017* includes fluoxetine (133).
- Specific types of antidepressants selected should carefully consider factors such as demographic

characteristics (e.g. higher risks and side-effects that may be associated with pregnancy or older age), side-effects profiles (e.g. sexual dysfunction, sleep problems, weight gain) and availability (e.g. continuous availability, costs).

- Explain rationale for prescribing and provide written and verbal information on benefits and harms, side-effects, drug interactions, the importance of taking medicines as prescribed and the likely time to improvement in symptoms.
- Regularly review the effectiveness of the medicine and side-effects with the person during the first three months of treatment and every three months afterwards. For adults who experience side-effects after starting medicine, consider closer monitoring of their symptoms, reducing the dose of the medicine or stopping the medicine gradually and offering alternative interventions.

DEP2. How long should treatment with antidepressants continue in adults with depressive episode/disorder?

Recommendation (update):

In adults with moderate-to-severe depression who have benefited from initial antidepressant treatment, continuation of the antidepressant treatment should be considered for at least six months after remission. Treatment should be regularly monitored, with special attention to treatment adherence, change in depressive symptoms and possible adverse effects.

Strength of recommendation: Conditional

Certainty of evidence: Very low

Justification

- Two meta-analyses contributed to the evidence profile: Kato et al., 2021 (40 RCTs) (134); Zhou et al., 2022 (40 RCTs) (135). One primary study (RCT) also contributed: Lewis et al., 2021 (136).
- Most of the difference in relapse rates (85.5%) between pharmacotherapy and placebo occurred in the first three months (63.9%) and first six months (another 22.6%). The difference in relapse-free rates becomes much smaller after six months.
- The relapse rate at one year was lower for pharmacotherapy compared with placebo. The

average of relapse-free months over a year was higher in the pharmacotherapy groups than in the placebo groups.

- The certainty of evidence for the mean difference in relapse rates between antidepressant medicines and pill placebo from 0 to 9 months, and relapse-free months at one year post-remission, response or recovery, is very low.
- The certainty of evidence is low for relapse rates at six months post-remission between antidepressants and pill placebo.

Remarks

- The term “depression” refers to moderate-to-severe depressive episode or disorder.
- The term “remission” is defined as relief from depressive symptoms.
- The studies identified in the review included people experiencing first or recurrent episodes of depression.
- Antidepressants are typically most effective in the initial 6–12 months and should only be continued where there is need and clinical oversight.

Research gaps

- Most of the research is from HICs. Further research is needed in LMICs.
- More research is needed to investigate the relationship between the number of depressive episodes and optimal treatment duration.
- More research is needed to examine the evidence to evaluate adverse effects regarding the duration of treatment.
- Further research is needed on how best to support individuals in managing withdrawal symptoms when stopping antidepressant medicines and guidance for clinicians on tapering of antidepressants and management of withdrawal symptoms.

Implementation considerations

- Long-term antidepressant use may be associated with additional adverse effects such as weight gain.
- Specific types of antidepressants selected should carefully consider factors such as demographic characteristics (e.g. higher risks that may be associated with pregnancy or older age) and side-effects profiles (e.g. sexual dysfunction, sleep problems, weight gain).
- When discontinuing antidepressants, abrupt discontinuation should be avoided and medicine doses should be tapered off slowly. Any withdrawal symptoms should be closely monitored.
- Providers should keep in mind the possible adverse effects associated with antidepressants, the ability to deliver either intervention (in terms of expertise, and/or treatment availability) and individual preferences. Discontinuities in drug availability (common in LMICs) may interfere with continuation of treatment.
- Costs accumulate with duration of prescription. Cost of daily dose of generic antidepressants varies from region to region throughout the world ranging between 3% and 9% of minimum wage (131).

DEP3. Is brief, structured psychological treatment better than (more effective than/as safe as) treatment as usual in adults with depressive episode/disorder?

Recommendation (update):	Structured psychological interventions should be offered for the treatment of adults with moderate-to-severe depression, namely behavioural activation therapy (BAT), brief psychodynamic therapy (DYN), cognitive behavioural therapy (CBT), interpersonal therapy (IPT), problem-solving therapy (PST) and third wave therapies (3WV). ⁷
Strength of recommendation:	Strong
Certainty of evidence:	Moderate

Justification

- Evidence was extracted from three meta-analyses: Cuijpers et al., 2021 (331 RCTs) (137); Karyotaki et al., 2021 (39 RCTs) (138); and Karyotaki et al., 2022 (11 RCTs) (139).
- A range of brief psychological treatments⁸ including guided/unguided internet-based CBT (iCBT) and task-shared psychological treatments were significantly better than treatment as usual (TAU) in reducing depressive symptoms.
- Life Review Therapy (LRT) and non-directive support counselling (SUP) were not included in the recommendation. For LRT, the certainty of evidence was low for reduction in depressive symptoms, treatment response and all-cause dropout, and very low for remission. SUP was less efficacious than all other therapies in one NMA.
- There were no significant differences between CBT, BAT, PST, 3WV, IPT, SUP, LRT and TAU in acceptability of treatment (all-cause dropout). DYN interventions had a significantly higher dropout rate than TAU.
- The brief structured psychological interventions included in the review delivered an average of 8–10 sessions (with a range of 1–20 sessions).
- Brief psychological interventions can be delivered effectively in different modalities (e.g. individual and group formats, internet-based) and through task sharing approaches. However, guided iCBT was more effective than unguided iCBT for people with moderate-to-severe depression.
- Promotion of the person's psychological skills (e.g. emotional, interpersonal, behavioural and cognitive skills) is a component of many brief psychological treatments for depressive episode/disorder. This has value beyond the reduction of depression.
- It is of value to include a range of brief psychological interventions in a non-specialized health-care package covering the treatment of depression to be able to respond to people's preferences.

Research gaps

- None of the studies included measured improvement in “quality of life and functioning” or “relapse” as outcomes.

Remarks

- The term “depression” covers moderate to severe depressive episode or disorder.

⁷ Third wave therapies included in the review are: mindfulness-based interventions, acceptance and commitment therapy, metacognitive therapy and dialectical behavioural therapy.

⁸ Brief psychological treatments included in this review are: CBT: cognitive behavioural therapy; iCBT: internet-based cognitive behavioural therapy; BAT: behavioural activation therapy; PST: problem-solving therapy; 3WV: third wave therapies; IPT: interpersonal therapy; DYN: brief psychodynamic therapy; SUP: non-directive support counselling; LRT: life review therapy.

Implementation considerations

- Psychological interventions can be delivered effectively in non-specialized health-care settings, as well as in other settings including specialized mental health care and social care.
- Face-to-face psychological interventions delivered by service providers is human resource-intensive as it requires substantial provider time, training and supervision.
- Regardless of severity, both guided and unguided interventions were more effective than TAU. However, the more severe symptoms the individual had, the better the effect of the guided psychological interventions (e.g. guided iCBT) compared with unguided. Unguided brief psychological interventions can be delivered without any therapist/service provider support, so they can be less resource intensive as well and may be an option for the treatment of depressive episode/disorder in non-specialized health-care settings if there are insufficient human resources for face-to-face/guided psychological treatment.
- Task sharing has been found to be an effective approach to delivering psychological interventions.
- Integrating the provision of psychological interventions into primary care provides many advantages, including more holistic health care, increased accessibility of mental health services for people in need of care, opportunities for reducing the stigma of mental health problems and reduced costs.
- Country adaptation and translation of training materials and tools for the provision of psychological interventions is essential.
- Psychological interventions have shown to be effective for people of different ages and genders.

DEP4. In adults with moderate-to-severe depressive disorder, what is the effectiveness and safety of antidepressant medicine compared with psychological treatment?

Recommendation (update):

In adults with moderate-to-severe depression, psychological interventions or combined treatment should be considered based on individual preferences and careful consideration of the balance of benefits and harms. Antidepressant medicine alone for adults with moderate-to-severe depression should only be considered when psychological interventions are not available. Providers should keep in mind the possible adverse effects associated with antidepressant medicines, and individual preferences.

Strength of recommendation: Conditional

Certainty of evidence: Low

Justification

- Evidence was extracted from two meta-analyses: Cuijpers et al., 2020 (101 studies) (140); and Furukawa et al., 2021 (81 RCTs) (141).
- Antidepressant medicines are as effective as psychological interventions in the short term in the treatment of depression. However, psychological interventions showed higher sustained response than antidepressants over the long term and antidepressants have more adverse effects.
- In terms of treatment efficacy, combined psychological interventions and antidepressants showed the best results across most of the analyses.
 - Combined treatment was better than pharmacotherapy alone in the reduction of depressive symptoms (SMD = 0.33), treatment response (RR = 1.25) and remission (RR = 1.23). These effects were sustained at 6–12 months follow-up (RR = 0.72), favouring combined treatment.

- Combined treatment was better than psychotherapy alone in the reduction of depressive symptoms (SMD = 0.30), treatment response (RR = 1.27) and remission (RR = 1.22). These effects were sustained at 6–12 months follow-up (RR = 0.84), favouring combined treatment.
- No significant differences were found between pharmacotherapy alone and psychological interventions alone in the reduction of depressive symptoms, treatment response and remission. However, psychological interventions were more effective than pharmacotherapy at 6–12 months follow-up (sustained response RR = 0.85).
- In terms of treatment efficacy for individuals with moderate depression, combined treatment had a significantly better treatment response compared with pharmacotherapy alone (RR = 1.23) and psychological interventions alone (RR = 1.19). No differences were found between psychological interventions alone and pharmacotherapy alone.
- In terms of treatment efficacy for individuals with severe depression, combined treatment had a better treatment response compared with pharmacotherapy alone (RR = 1.09). There were no differences between psychotherapy alone and pharmacotherapy alone, and between combined therapy and psychological interventions alone.
- In terms of treatment acceptability, all-cause study dropout was significantly better for combined treatment compared with pharmacotherapy alone (RR = 1.23). Psychotherapy alone also had higher acceptability rates compared with pharmacotherapy alone (RR = 1.17). No significant differences were found between combined treatment and psychological interventions regarding treatment acceptability.

Remarks

- The term “combined treatment” refers to psychological interventions provided together with antidepressant medicines.
- Psychological interventions include BAT, DYN, CBT, IPT, PST and 3WV. The review focused on psychological interventions delivered by mental health professionals.
- Antidepressants include SSRIs (e.g. citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine or sertraline) and TCAs (e.g. amitriptyline and clomipramine).

Research gaps

- Most of the evidence (80%) is from HICs.

Implementation considerations

- Face-to-face psychological interventions delivered by service providers are human resource-intensive as they require substantial provider time, training and supervision.
- Both generic TCAs and many generic SSRIs are associated with low acquisition costs.
- Discontinuities in drug availability (common in LMICs) may interfere with continuation of treatment.
- Service providers should help the person make decisions about available treatments, based on providing relevant information (e.g. possible side-effects, costs).
- A stepped care treatment approach may be considered offering psychological interventions first. If the person does not improve with psychological interventions, combined treatment can be considered based on individual preferences and careful consideration of the balance of benefits and harms.

3.7 Drug use disorders (DRU)



DRU1. Are brief psychosocial interventions for people using cannabis or stimulants effective in reducing drug use, dependence and harm from drug use?

Recommendation (update):	1.1 Adults using cannabis should be offered screening and brief intervention. Brief intervention should comprise at least a single session, incorporating individualized feedback and advice on reducing or stopping cannabis consumption, and the offer of follow-up care.
	Strength of recommendation: Strong
	Certainty of evidence: Very low
	1.2 Adults using psychostimulants should be offered screening and brief intervention. Brief intervention should comprise at least a single session, incorporating individualized feedback and advice on reducing or stopping psychostimulant consumption, and the offer of follow-up care.
	Strength of recommendation: Strong
	Certainty of evidence: Very low
	1.3 For adults with hazardous cannabis or psychostimulant use, or with disorders due to use of these substances who do not respond to brief interventions, referral for specialist intervention should be considered.
	Strength of recommendation: Conditional
	Certainty of evidence: Very low

Justification

- Evidence was extracted from a systematic review by Arcadepani et al., 2023 (23 studies)⁹ that was conducted to update an earlier systematic review by Chou et al., 2020 (20 studies) (142).
- In adults with cannabis use, brief interventions, in comparison with minimal intervention (or waitlist), show effect for: increasing abstinence at 3- to 4-month follow-up (RR = 2.08; 95% CI: 1.51 to 3.07; very low certainty); increasing abstinence at 6- to 12-month follow-up (RR = 1.58; 95% CI: 1.17 to 3.06; very low certainty).

In adults with psychostimulant use, brief interventions, in comparison with minimal intervention (or waitlist), show effect for: increasing abstinence at 6- to 12-months follow-up (RR = 1.25; 95% CI: 1.11 to 1.52; very low certainty).

- A strong recommendation was suggested despite very low certainty of evidence due to potential public health benefits of increasing identification of people who might benefit from simple advice and referral to treatment.
- Suggestion to separate cannabis and psychostimulants into two separate

⁹ Arcadepani FB, Fidalgo TM, Bisaga A. Are brief psychosocial interventions for people using cannabis and/or stimulants effective in reducing drug use, dependence and harm from drug use? 2023 (in preparation).

recommendations/statements was made during a technical expert group meeting due to substantial differences in pharmacological effects, clinical manifestations and treatment approaches.

Remarks

- About 209 million people use cannabis (143) and there are about 24 million people with cannabis use disorders globally (144). While it is estimated that around 1 in 10 cannabis users (and half of daily cannabis users) develop cannabis dependence (145), cannabis use is associated with well documented health risks or harms even for those not meeting criteria for cannabis dependence, including increased risks of negative mental health outcomes (decline in cognitive function, social and educational outcomes, psychosis, mood disorders), physical health (respiratory, cardiovascular diseases, cancer), road traffic accidents and more (146).
- Considering high prevalence and well documented health risks associated with cannabis use, wider implementation and scale up of simple advice, brief interventions and, when appropriate, offer of referral to treatment can result in significant health gains at population level.
- Use of cannabis or psychostimulants in the recommendation refers to the use of substances without medical prescription. Psychostimulants considered in the recommendations include cocaine and amphetamine-type stimulants.
- In ICD-11, hazardous use refers to a pattern of substance use that appreciably increases the risk of harmful (physical or mental) health consequences to the user or to others to an extent that warrants attention and advice from health professionals. The increased risk may be from the frequency of substance use, from the amount used on a given occasion, from risky behaviours associated with substance use or the context of use, from a harmful route of administration, or from a combination of these. The risk may be related to short-term effects of the substance or to longer-term cumulative effects on physical or mental health or functioning. Hazardous drug use has not yet reached the level of having caused harm to physical or mental health of the user or others around the user.
- In ICD-11, harmful use refers a pattern of substance use that has caused damage to a person's physical or mental health or has resulted in behaviour leading to harm to the health of others. The pattern of drug use is evident over a period of at least 12 months if substance use is episodic or at least one month if use is continuous (i.e. daily or almost daily). Harm to the health of the individual occurs due to one or more of the following: (i) behaviour related to intoxication; (ii) direct or secondary toxic effects on body organs and systems; or (iii) a harmful route of administration. Harm to health of others includes any form of physical harm, including trauma or mental disorder that is directly attributable to behaviour related to substance intoxication on the part of the person to whom the diagnosis of harmful pattern of use applies.
- Screening refers to asking about drug use with an aim to detect health problems or risks at an early stage before they have caused serious disease or other problems. It includes screening by using standardized instruments but does not refer to testing of biological fluids for the presence of drugs.
- The term "brief interventions" refers to a structured, time-limited approach aiming to help individuals reduce or stop substance use. Its intensity and duration ranges from a single short conversation to a few sessions, not necessarily linked to the use of a specific screening instrument.
- Brief interventions are often designed to be delivered opportunistically in most settings, including primary care where people may be seeking help for problems unrelated to substance use and which can be delivered by professionals with limited training, thus facilitating access to interventions for a large number of individuals.
- Any treatment or support for people using drugs or with drug use disorders should ensure ethical standards – including respect for human rights and the individual's dignity, and never using humiliating or degrading interventions – in line with the WHO and United Nations Office on Drugs and Crime (UNODC) *International standards for the treatment of drug use disorders* (147), as shown in **Box 3.1**.

BOX 3.1 Ethical standards for providing treatment of support to people using drugs or with drug use disorders

- ▶ The patients should grant informed consent before treatment begins and have a guaranteed option to withdraw from treatment at any time.
- ▶ Patient data should be strictly confidential. Circumventing the confidentiality of health records in order to register patients entering treatment should be prohibited.
- ▶ Legislative measures, supported by appropriate staff training and service rules and regulations, should ensure and protect the confidentiality of patient data.
- ▶ Staff of treatment services should receive proper training in the delivery of treatment in full compliance with ethical standards and human rights principles, and show respectful, non-stigmatizing and non-discriminatory attitudes towards service-users.
- ▶ Service procedures should require staff to adequately inform patients of treatment processes and procedures, including their right to withdraw from treatment at any time.

Source: WHO and UNODC, 2020 (147).



Research gaps

- Most of the studies were done in HICs. Further research is needed in LMICs.
- There were more studies on cannabis use: 12 specifically on cannabis use and 10 on both cannabis and psychostimulants, while only one study specifically focused on psychostimulant use.
- Only two studies were performed in the emergency department. Further research is needed on this setting.
- Evidence of effectiveness remains primarily extracted from trials conducted in treatment-seeking populations.
- There is not enough evidence to assess the balance of benefits and harms of screening for drug use in adolescents.

Implementation considerations

- Brief intervention programmes are of low intensity with respect to human resources and training, making them suitable for low-resource settings. In addition, they can be conducted in a variety of settings, including non-medical settings, and can be given opportunistically to people who are not in formal drug treatment. Brief intervention programmes are suitable for LMICs.
- Screening and brief interventions should ideally

be provided in settings where services for detailed assessment, diagnosis, treatment and appropriate care can be offered or in settings when referral to further services can be arranged. However, in some settings services for those with positive screening results might be limited or unaffordable. All efforts should be made to offer additional support to people with positive results of screening.

- Screening for drug use and drug use disorders might increase detection of substance use disorders but has a number of potential implications. In some countries, health practitioners can be pressured to forward this information to the police or other authorities. Clinicians should be aware and cautious of the potential implications for individuals screened positively in a given jurisdiction and offer interventions on the basis of informed consent and confidentiality.
- Integrating the provision of brief interventions into primary care provides many advantages, including more holistic health care, increased accessibility of mental health services for people in need of care, opportunities for reducing the stigma of mental health problems and reduced costs.
- It is important to ensure availability, acceptability and country adaptation of training materials and tools for the provision of brief interventions.

DRU2. Are pharmacotherapies safe and effective for the treatment of cocaine or stimulant dependence?

Recommendation (update):	Dexamphetamine, methylphenidate and modafinil are not recommended for the treatment of cocaine or stimulant use disorders due to safety concerns.	
	Strength of recommendation:	Conditional
	Certainty of evidence:	Low

Justification

- The systematic reviews that provided information were divided into two categories, according to drug of abuse:
 - cocaine: Tardelli et al., 2020 (148); Nourredine et al., 2021 (149); Chan et al., 2020 (150); Buchholz and Saxon, 2019 (151); Chan et al., 2019 (152); Fluyau et al., 2021 (153); and
 - methamphetamine: Tardelli et al., 2020 (148); Siefried et al., 2020 (154); Naji et al., 2022 (155); Nourredine et al., 2021 (149); Chan et al., 2020 (150); Fluyau et al., 2021 (153); Chan et al., 2019 (152); Lam et al., 2019 (156).
 - Note: The reviews by Tardelli et al. (148), Chan et al. (150), Nourredine et al. (149) and Fluyau et al. (153) included both cocaine and methamphetamine.
- In adults with cocaine dependence, compared with no treatment or treatment as usual (TAU), there is inconsistent or no evidence for effectiveness of: naltrexone (very low certainty), modafinil (low to very low certainty), methylphenidate (very low to moderate certainty) or mirtazapine (very low certainty) in terms of reducing drug use, promoting abstinence, reducing harm from drug use or improving retention to treatment.
- In adults with stimulant dependence, compared with no treatment or TAU, there is controversial or no evidence for effectiveness of use of topiramate (low to moderate certainty); naltrexone (low to very low certainty); modafinil (low certainty); prescription

- amphetamines/dexamphetamine (low to very low certainty); methylphenidate (very low to moderate certainty); mirtazapine (very low certainty) or bupropion (low certainty) in terms of reducing drug consumption, promoting abstinence, reducing harm from drug use or improving retention to treatment.
- In adults with cocaine dependence, compared with no treatment or TAU, there is some evidence for effectiveness of: topiramate for increasing abstinence in some studies (very low to moderate certainty); prescription amphetamines/dexamphetamine for increasing abstinence (RR = 2.44; 95% CI: 1.66 to 3.58; moderate certainty); bupropion for increasing abstinence (RR = 1.63; 95% CI: 1.03 to 2.59; very low certainty).
- In adults with cocaine dependence, compared with no treatment or TAU, there is limited evidence that bupropion can potentially worsen treatment retention due to adverse effects (very low certainty).
- Despite presence of some evidence of effectiveness of topiramate, prescription amphetamines/dexamphetamine and bupropion, it was decided not to recommend their use due to limited data on effectiveness, safety and absence of studies in non-specialized settings.
- Some medicines might have severe side effects and have potential for abuse (such as dexamphetamines, methylphenidate, modafinil) and require careful monitoring, which might be difficult to achieve in non-specialized settings; their use should therefore be discouraged.

Remarks

- There is insufficient evidence to support use of naltrexone, dexamphetamine, methylphenidate, modafinil, topiramate, mirtazapine or bupropion for the treatment of stimulant use disorders in non-specialized settings.
- The term “cocaine or stimulant use disorders” refers to diagnosis according to the ICD-10, DSM-IV criteria or equivalent ICD-11 and DSM-5 diagnosis.
- Pharmacological treatment considered in the current review included: naltrexone, dexamphetamine, methylphenidate, modafinil, topiramate, mirtazapine and bupropion.
- Most of the trials using above medicines had elevated dropout rates which severely impacted their results.
- Mirtazapine is a promising alternative that was found to have a relevant impact on subgroups (cisgender men and transgender women who have sex with men).
- The combination of depot naltrexone and bupropion had a small but statistically significant impact on methamphetamine use in a recent trial.
- Any treatment or support for people using drugs or with drug use disorders should ensure ethical standards – including respect for human rights and the individual’s dignity, and never using humiliating or degrading interventions – in line with the WHO and UNODC *International standards for the treatment of drug use disorders* (147) (see [Box 3.1](#)).

Research gaps

- All studies were done in HICs. Further research is needed in LMICs.
- Most trials assessed adult populations, excluding individuals under 18 or above 70 years old. Further research is needed on adolescents and older adults.
- Evidence on prescription amphetamines/ dexamphetamine is very limited, as few studies assessed them for methamphetamine dependence, with heterogeneous outcomes. Evidence on prescription amphetamines for cocaine dependence is limited by earlier trials that used very small doses. Further research is needed.

- There are no studies in non-specialized settings. Further research in these settings would be beneficial in understanding feasibility, acceptability and effectiveness.
- Most of the evidence is of low or very low quality with high levels of uncertainty. This is very much attributable to the high dropout rates observed in most of the trials, and lack of data on techniques to reduce attrition.

Implementation considerations

- Some medicines have potential for abuse and adverse effects (such as prescription amphetamines/ dexamphetamine and methylphenidate).
- Service providers should assess psychosocial stressors (e.g. domestic abuse, unemployment) associated with methamphetamine or cocaine use and dependence and include appropriate psychosocial interventions in their treatment plan.
- The costs of the medicines evaluated here can vary between countries. There is very little literature on cost-effectiveness and pharmacoeconomic aspects in general for medicines to treat methamphetamine dependence.
- If implemented, any psychopharmacological treatment of stimulant dependence should carefully consider the specific clinical characteristics of each person receiving the treatment (e.g. higher risk of psychotic episodes with prescription psychostimulants among individuals with previous history of psychosis). The medicine choice should consider, besides effectiveness, factors such as demographic characteristics (e.g. higher risks and side-effects that may be associated with pregnancy or older age), side-effects profiles (e.g. cardiovascular effects, psychosis/mania, weight gain) and availability (e.g. continuous availability, costs).
- Comorbidities and complications, namely cardiovascular events and psychosis, should be carefully monitored during the treatment of methamphetamine dependence.

DRU3. Which psychosocial interventions are effective in the treatment of stimulant dependence for adults?

Recommendation (update):	Psychosocial interventions – namely cognitive behavioural therapy (CBT) and contingency management – should be offered to adults with cocaine and stimulant dependence.	
	Strength of recommendation:	Strong
	Certainty of evidence:	Low

Justification

- Evidence was extracted from a new systematic review by Minozzi et al., 2023 (65 RCTs).¹⁰ This is an update to an earlier Cochrane Review by Minozzi et al., 2016 (157).
- In adults with stimulant dependence, any psychosocial interventions:
 - compared with no treatment, show effect for: decreasing dropouts from study and frequency of drug intake, increasing longest period of abstinence (moderate certainty), and increasing continuous abstinence at the end of treatment (low certainty);
 - compared with no treatment, show little to no difference for: point abstinence at the end of treatment (high certainty), and point abstinence and continuous abstinence at longest follow-up (low certainty);
 - compared with TAU, show effect for: decreasing dropouts from treatment (moderate certainty), and increasing point abstinence at the end of treatment and at longest follow-up (very low certainty);
 - compared with TAU, show little to no difference for: continuous abstinence at end of treatment (low certainty), increasing continuous abstinence at longest follow-up, and longest period of abstinence (very low certainty).
- In adults with stimulant dependence, CBT:
 - compared with no treatment, shows effect for: increasing continuous abstinence at the end of treatment, and increasing longest period of abstinence (moderate certainty);
 - compared with no treatment, shows little to no difference for: dropout from study and point abstinence at the end of treatment (moderate certainty), point (high certainty) and continuous abstinence at longest follow-up (very low certainty), and frequency of drug intake at longest follow-up (low certainty);
 - compared with TAU, shows effect for: decreasing dropouts, increasing point abstinence at longest follow-up (low certainty), probably increasing point abstinence at the end of treatment (RR = 1.73; 95% CI: 0.99 to 3.02), and decreasing frequency of drug intake (very low certainty);
 - compared with TAU, shows little to no effect for: continuous abstinence at the end of treatment and on longest period of abstinence (very low certainty).
- In adults with stimulant dependence, contingency management:
 - compared with no treatment, shows effect for: reducing dropouts (low certainty), increasing continuous abstinence at the end of treatment and point abstinence at longest follow-up, increasing longest period of abstinence, and decreasing frequency of drug intake (moderate certainty);
 - compared with no treatment, shows little to no difference for: point abstinence at the end of treatment (low certainty), and point and continuous abstinence at longest follow-up (very low certainty);
 - compared with TAU, shows effect for: probably reducing dropouts and increasing point

¹⁰ Minozzi, S. Which psychosocial interventions are effective in the treatment of stimulant dependence for adults? 2023 (in preparation).

abstinence at the end of treatment and longest follow-up (low to very low certainty).

- In adults with stimulant dependence, motivational interviewing:
 - compared with no treatment, shows effect for: probably reducing frequency of drug intake (SMD = 0.18 lower; 0.38 lower to 0.03 higher; moderate certainty);
 - compared with no treatment, shows little to no difference for: dropouts; point abstinence at longest follow-up (low certainty), and continuous abstinence at longest follow-up (very low certainty);
 - compared with TAU, shows little to no difference for: frequency of drug intake at the end of treatment (low certainty) and dropouts (very low certainty).
- In adults with stimulant dependence, psychodynamic therapy:
 - compared with no treatment, shows effect for: probably reducing dropouts (RR = 0.87; 95% CI: 0.74 to 1.01; moderate certainty);
 - compared with no treatment, shows little to no difference for: point abstinence at the end of treatment and at longest follow-up (moderate certainty).
- In adults with stimulant dependence, individual counselling:
 - compared with no treatment, shows effect for: probably increasing point abstinence at the end of treatment (RR = 1.26; 95% CI: 1.00 to 1.59; moderate certainty);
 - compared with no treatment, shows little to no difference for: point abstinence at longest follow-up (moderate certainty).
- In adults with stimulant dependence, positive affect therapy:
 - compared with no treatment, shows effect for: probably reducing frequency of drug intake at longest follow-up (SMD = 0.29 lower; 0.56 lower to 0.02 lower; moderate certainty).
- It is unclear whether 12-step approach has effect on adults with stimulant dependence, compared with no treatment or TAU.
- In adults with stimulant dependence, it is uncertain if any psychosocial interventions, compared with no treatment or TAU, have any effect on frequency of adverse events and depression.

- In adults with stimulant dependence, head-to-head comparison of different interventions (from 15 studies) shows no difference, except for CBT, compared with individual counselling, showing effect for: probably decreasing dropouts (RR = 0.86; 95% CI: 0.74 to 1.01) and point abstinence at the end of treatment (moderate certainty).

Remarks

- The term “cocaine and stimulants dependence” refers to diagnosis according to the ICD-10 or DSM-IV criteria or equivalent ICD-11 and DSM-5 diagnosis.
- Psychosocial interventions considered in the current review included: cognitive behavioural approach (including: cognitive therapy, community reinforcement approach, coping skills training [CST], relapse prevention), contingency management approach, motivational interviewing approach (motivational interviewing, motivational enhancement), IPT approach, psychodynamic therapy and supportive expressive therapy and the 12-step approach. It included studies if they considered the above treatments alone or in combination with other types of treatment. Focus was on included structured and standardized interventions targeting individual, case management and counselling that are usually provided in standard care (TAU), so the review did not consider them among the experimental interventions. Similarly, family or couples-therapy was not included in the review, as they do not target only individuals but involve people in their close environment. The review excluded studies that compared the same type of intervention as a different modality or at a different intensity (e.g. intensive versus standard, group versus individual, long versus short).
- Any treatment or support for people using drugs or with drug use disorders should ensure ethical standards – including respect for human rights and the individual’s dignity, and never using humiliating or degrading interventions – in line with the WHO and UNODC *International standards for the treatment of drug use disorders* (147) (see [Box 3.1](#)).

Research gaps

- Most of the studies were done in HICs. Further research is needed in LMICs.
- There was a relatively low number of studies on some interventions: 12-step approach (4 studies);

IPT (3 studies); positive affect intervention (1 study); psychodynamic therapy (1 study). Further research is needed to understand the balance of risks and benefits for these interventions.

Implementation considerations

- Face-to-face psychosocial interventions delivered by service providers are human resource-intensive as they require substantial provider time, training and supervision.
 - Psychosocial interventions can be delivered effectively in non-specialized health-care settings if proper training to health professionals is provided,
- as well as in other settings, including specialized services for mental and substance use disorders.
 - Integrating the provision of psychosocial interventions into primary care provides many advantages, including more holistic health care, increased accessibility of mental health services for people in need of care, opportunities for reducing the stigma of mental health problems and reduced costs.
 - Country adaptation and translation of training materials and tools for the provision of psychosocial interventions is essential.

DRU4. In adults with drug use disorders or using drugs, are digital or telemedicine interventions effective?

Recommendation (new):	Digital interventions should be considered for adults using drugs or with drug use disorders. They should not replace provision of other forms of interventions and should ensure informed consent, safety, confidentiality, privacy and security.	
	Strength of recommendation:	Conditional
	Certainty of evidence:	Very low

Justification

- Evidence was extracted from a systematic review: Boumparis et al., 2023 (49 RCTs).¹¹
 - In adults with cannabis use disorders or those using cannabis, digital interventions, when compared with non-active (waitlist, assessment-only) and active (TAU, brief interventions) comparators, show effect for reducing cannabis use (very low certainty).
 - In adults with any drug use disorders or those using drugs, it is uncertain if digital interventions, when compared with non-active (waitlist, assessment-only) comparators, have effect for reducing drug use (very low certainty).
 - In adults with stimulant use disorders or those using psychostimulants, it is uncertain if digital interventions, when compared with non-active (waitlist, assessment-only) comparators, have
- effect for reducing psychostimulant use (very low certainty).
 - There were no studies examining the effect of digital interventions among people with opioid use disorders or using opioids compared with non-active comparators.
 - In adults with any drug use disorder or those using drugs, digital interventions, when compared with active (TAU, brief interventions) comparators, show effect for reducing any drug use (very low certainty).
 - In adults with any stimulant use disorders or those using psychostimulants, digital interventions, when compared with active (TAU, brief interventions) comparators, show effect for reducing psychostimulant use (very low certainty).
 - In adults with opioid use disorders or those using opioids, digital interventions, when compared

11 Boumparis N, Khazaal Y, Krupchanka D, Schaub MP. Digital interventions for adult drug users: a systematic review and meta-analysis. 2023 (in preparation).

with active (TAU, brief interventions) comparators, show effect for reducing opioid use (very low certainty).

Remarks

- The term “drug use disorders”, “cannabis use disorders”, “stimulant use disorders”, “opioid use disorders” refers to diagnosis according to the ICD-10 or DSM-IV criteria or equivalent ICD-11 and DSM-5 diagnosis.
- By the term “any drug use”, we refer to studies recruiting participants who use at least one psychoactive drug and are included in interventions targeting substance use reduction regardless of the primary drug.
- The included digital interventions encompass unguided digital interventions, in which psychoeducation and psychotherapeutic techniques are provided for the individual to self-manage their symptoms without the help of a health worker. In guided digital interventions, additional guidance is provided to assist participants with technical or health-related questions via chat, email or telephone.
- Studies that assess the reduction of any drug use via digital interventions compared with non-active comparators are usually recruiting individuals from settings in which brief interventions are conducted. These settings commonly include hospitals, primary care clinics and community health centres. The majority of those interventions consist of very brief screenings and brief interventions lasting up to 30 minutes.
- The studies assessing the reduction of drug use via digital interventions compared with active comparators are usually recruiting individuals from specialized treatment facilities. The majority of those interventions combine the digital component with face-to-face treatments, such as TAU or CBT, and last 8–12 weeks.
- Differences in findings between active/non-active comparators should be interpreted with caution. For the comparisons involving non-active comparators, the majority of individuals were recruited based on self-reported use patterns and not assessed for a substance use disorder. This is contrary to the studies involving active comparators that recruited participants after the diagnosis of a substance use disorder. For this reason, it is important to stress that

different findings for active/non-active comparators are likely due to the different characteristics (such as severity) of the target group and intensity of the provided treatment.

- While the evidence is limited, it is possible that individuals with a substance use disorder who receive TAU in addition to a digital intervention benefit more from the digital component. This is particularly relevant for individuals with drug use disorders.
- While digital health interventions show effectiveness and can enhance access to health services, they should not be used to replace or detract from provision of other forms of interventions and should ensure patients’ free and informed consent, safety, confidentiality, privacy and security.
- Any treatment or support for people using drugs or with drug use disorders should ensure ethical standards – including respect for human rights and the individual’s dignity, and never using humiliating or degrading interventions – in line with the WHO and UNODC *International standards for the treatment of drug use disorders* (147) (see [Box 3.1](#)).

Research gaps

- The certainty of evidence for reduction in drug use (compared with non-active and active comparators) was very low, mainly due to the limited number of available studies and their high risk of bias. Further research is needed to understand the outcome of reduction in drug use.
- Subgroup analyses did not show significant differences between groups (guided vs unguided interventions, drug use disorders vs no drug use disorders). However, the ability to perform subgroup analyses was limited due to the small number of studies in the different conditions and types of interventions.
- Most studies are from HICs. Further research is needed on LMICs.
- There is a lack of an established gold standard for reporting drug use outcomes. Further development of this would aid consistency of reporting in the field.
- There are not enough data to understand the role of digital interventions for equity, equality and non-discrimination of people using substances: while there is a potential of increasing access to care, it is also possible that not all people can benefit

from it due to the “digital divide”, which requires further research.

Implementation considerations

- Digital interventions can provide benefits to people using drugs and with drug use disorders, especially when provided in addition to TAU. They should not substitute provision of other types of conventional treatment (psychosocial or pharmacological) to people with drug use disorders. When face-to-face treatment is not available or acceptable, self-help digital interventions can be a feasible option to provide support.
- There are concerns regarding potentially sensitive content and data privacy while using digital health interventions. Measures should be taken ensuring that digital interventions are provided under conditions of safety/security, confidentiality, informed consent and privacy of data. This can include the establishment of standard operating

procedures that describe protocols for ensuring patient consent, data protection and storage, and verifying provider licensing and credentials. Further guidance can be found in the 2019 *WHO guideline: recommendations on digital interventions for health system strengthening* (31).

- There might be an issue with potential digital divide across population groups having unequal access to and skills to use digital technologies. Access might be particularly difficult for certain population groups with poor access to network services, mobile devices or electricity, and/or with low literacy and digital literacy skills. Measures should be taken to address inequities in access to mobile devices so that further inequity is not perpetuated in accessing health information and services, including mechanisms to ensure individuals who do not have access to mobile devices can still receive appropriate services.
- Country adaptation and translation of digital interventions tools is essential.

DRU5. In adults with drug dependence, are recovery-oriented services effective?

Recommendation (new):	Recovery-oriented services on a voluntary basis should be considered for adults with drug-dependence. Namely, case management, long-term residential and continuing community care approaches, occupation-based therapies and peer support groups should be considered for recovery management of people with drug dependence.
Strength of recommendation:	Conditional
Certainty of evidence:	Low

Justification

- Evidence was extracted from 25 systematic reviews that included different recovery-oriented interventions: Ashford et al., 2019 (158); Nesvag and McKay, 2018 (159); Wasmuth et al., 2016 (160); Giménez-Meseguer et al., 2020 (161); Sancho et al., 2018 (162); Beraldo et al., 2019 (163); Walton-Moss et al., 2013 (164); Vest et al., 2021 (165); Magura and Marshall, 2020 (166); Harrison et al., 2020 (167); Akanbi et al., 2020 (168); Vanderplasschen et al., 2019 (169); Eddie et al., 2019 (170); Reif et al., 2014 (171); Tracy and Wallace, 2016 (172); Gormley et al.,

2021 (173); Orock and Nicette, 2022 (174); Bassuk et al., 2016 (175); Beck et al., 2017 (176); de Andrade et al., 2019 (177); Penzenstadler et al., 2019 (178); Beaulieu et al., 2021 (179); Austin et al., 2021 (180); Reif et al., 2014 (181); du Plessis et al., 2020 (182).

- In adults with drug dependence, compared with no treatment or TAU, there is controversial or limited evidence for effectiveness of the following recovery-oriented services: (i) digital recovery support (very low certainty); (ii) physical exercise (effect on general health (moderate certainty), no direct evidence on critical outcomes); (iii) mindfulness based (no

evaluation of critical outcomes); (iv) spirituality/religiosity (no evaluation of critical outcomes or lack of good studies); (v) college recovery programmes (lack of methodological quality, heterogeneity); (vi) employment support (no measures of critical outcomes, no employment-related outcomes, no rigorous evaluation of substance use outcomes); (vii) SMART (Self-Management and Recovery Training) recovery (very low certainty); (viii) peer support workers (no critical outcomes evaluated); (ix) residential treatment services (methodological flaws); (x) assertive community treatment (high heterogeneity); (xi) housing (no critical outcomes evaluated and low certainty).

- In adults with drug dependence, compared with no treatment or TAU, there is some evidence for effectiveness of the following recovery-oriented services: (i) case management for substance use disorders (moderate for substance-use-related outcomes); (ii) peer support groups (abstinence [moderate certainty] but not for all substances [opioids questioned in some]); (iii) long-term treatment and support for abstinence (high certainty).

Remarks

- The term “drug dependence” refers to diagnosis according to the ICD-10 or DSM-IV criteria or equivalent ICD-11 and DSM-5 diagnosis.
- Recovery is “a continuum process and experience through which individuals, families, and communities utilize internal and external resources to address substance use disorders, actively manage their continued vulnerability to such disorders, and develop a healthy, productive and meaningful life”, according to the WHO and UNODC *International standards for the treatment of drug use disorders* (147).
- Recovery-oriented interventions considered in current review included: digital recovery support, user-involvement/oriented care models (spiritual/religious interventions, role of self-care, mindfulness-based therapies, physical exercise, occupational therapy), employment (individual placement and support [IPS]), recovery-oriented systems of care (peer recovery support services [PRSS], case management, assertive community treatment [ACT]), long-term approaches, housing and family support.

- Case management refers to a client-centred approach to improve the coordination and continuity of service delivery for people with substance use disorders. This approach supports individuals by helping them identify needed services, facilitate linkage with services and promote participation and retention in services. Long-term continuing community care approaches (also called “aftercare”, “recovery management”) refer to services supporting people with drug use disorders in the process of gradually increasing health and wellness, as well as assisting them in recovery, reducing the risk of relapse to substance use by comprehensively supporting social functioning and well-being, as well as social reintegration into the community and society. This might include, but is not limited to, recovery management check-ups, help with management of stressful situations and engagement in the community, peer recovery support and other interventions that gradually increase social reintegration and improve chances of stable remission and recovery, according to the WHO and UNODC *International standards for the treatment of drug use disorders* (147).
- Long-term residential approaches refer to services for individuals with drug use disorders living in a communal environment with others and participating in an intensive daily programme. The programmes provide a diverse range of interventions such as: community meetings and group work; individual psychosocial interventions; family psychosocial interventions; mutual aid and self-help; active participation in community life; and gaining life skills and vocational training. Long-term residential programmes, especially therapeutic communities, use the programme’s entire community, including other residents and staff, as active components of treatment and recovery management, according to the WHO and UNODC *International standards for the treatment of drug use disorders* (147).
- Occupation-based therapies refer to those interventions in which an occupation or activity is performed with the aim of structuring time and creating meaning in one’s life, for example in areas of education, work, leisure and social participation. Occupational therapies help to develop skills necessary to address deficits in occupational performance, promote development of healthy

performance patterns and environmental contexts that support abstinence or the reduction of alcohol and drug use.

- Any treatment or support for people using drugs or with drug use disorders should ensure ethical standards – including respect for human rights and the individual’s dignity, and never using humiliating or degrading interventions – in line with the WHO and UNODC *International standards for the treatment of drug use disorders* (147) (see [Box 3.1](#)).

Research gaps

- The majority of studies were conducted in HICs. Further research is needed in LMICs.
- Overall, there is a lack of standard definitions for interventions used in recovery-oriented services, high heterogeneity of outcome measures and diversity of study methods that substantially hamper rigorous evaluation of effectiveness of treatment approaches.
- The primary outcome for long-term (18 months or more) treatment was abstinence; improvement was in favour of the long-term treatment group. Abstinence is a dichotomous outcome and a very high threshold to achieve for people with high severity of substance use disorder. Therefore, it is possible that if other recovery outcomes were assessed, additional positive impact could be found, highlighting the need for more research on this topic.

Implementation considerations

- Although identifying evidence on the costs of implementation was beyond the scope of the systematic reviews conducted for this update, face-to-face psychosocial interventions delivered by service providers are human resource-intensive as these require substantial provider time, training and supervision.

- The costs of long-term treatment are likely greater than for short-term approaches, but no data on this topic were available in the reviews.
- Though there are not enough studies in primary care, many interventions can be delivered effectively in non-specialized health-care settings but also in other settings including specialized mental health care and social care with a role of trained peers. Integrating the provision of interventions into primary care provides many advantages, including more holistic health care, increased accessibility of mental health services for people in need of care, opportunities for reducing the stigma of mental health problems and reduced costs.
- Decision on the choice and implementation of recovery-oriented services should be based on individual characteristics of a person and be adjusted to the complexity of each person’s needs. Service providers should help the person navigate through the system and make informed decisions about engagement into various activities on a case-by-case basis. Country adaptation and translation of training materials and tools for the provision of psychosocial interventions is essential.
- There is no identifiable conflict regarding sociocultural differences in most interventions, however, some spiritually oriented interventions can be culture-sensitive.
- Peer support integrates treatment approaches with the cultural context of each population, integrating the community and reducing the gap between people affected by the condition and those who have already managed to overcome it, thus reducing the stigma. The fact that people from the community are involved in peer support leads to a more culturally appropriate approach.

3.8 Epilepsy and seizures (EPI)



EPI1. In adults with established status epilepticus, i.e. seizures persisting after the first-line agent (benzodiazepine-resistant status epilepticus), which antiseizure medicines are associated with better clinical outcomes (stopping seizures and with less adverse effects)?

Recommendation (update):

In adults with established status epilepticus, i.e. seizures persisting after two doses of benzodiazepines, either intravenous fosphenytoin, intravenous phenytoin, intravenous levetiracetam, intravenous phenobarbital or intravenous valproic acid (sodium valproate) should be considered with appropriate monitoring. The choice of these medicines depends on local resources, including availability and facilities for monitoring.

Strength of recommendation: Conditional

Certainty of evidence: Low

Justification

- A new systematic review was conducted: Sharma et al., 2023 (8 RCTs).¹²
- There is low- to moderate-quality evidence that there is no clinically important difference in efficacy between intravenous fosphenytoin, levetiracetam, phenytoin or sodium valproate for the treatment of benzodiazepine-resistant status epilepticus in adults. There is low-quality evidence that phenobarbital may be more effective than sodium valproate in the treatment of benzodiazepine-resistant status epilepticus in adults.
- There is low- to moderate-quality evidence that the safety profile of levetiracetam was better than fosphenytoin, in terms of lesser cardiovascular adverse events. There is low-quality evidence that phenobarbital has a higher risk of respiratory depression and cardiovascular adverse effects as compared with sodium valproate.
- Another factor of concern is the speed of administration. Fosphenytoin, levetiracetam and sodium valproate can be administered within 10 minutes, whereas phenobarbital and phenytoin need to be infused over 20 minutes. Time is of the essence while treating status epilepticus.

- There is insufficient evidence to recommend lacosamide and diazepam infusion at this time.

Remarks

- Status epilepticus is a medical emergency which can lead to profound systemic and neurological damage and is associated with significant short-term and long-term mortality. Timely control of status epilepticus is of paramount importance to improve the outcomes.
- A staged treatment protocol for management of status epilepticus is recommended.
 - Approximately 30–40% of all individuals fail to respond to initial treatment with benzodiazepines (benzodiazepine-resistant or established status epilepticus) and need further treatment with other intravenous antiseizure medicines (ASMs). The treatment of established status epilepticus is the focus of this recommendation with the above medicines initiated when seizures persist after two doses of benzodiazepines.
- Advantages of levetiracetam and sodium valproate include lesser risk of adverse effects as compared with fosphenytoin. Both levetiracetam and sodium valproate are broad spectrum medicines active

¹² Sharma S, Jain P, Aneja S. Antiseizure medicine treatment for established status epilepticus in adults. 2023 (in preparation).

against all types of seizures, and hence may be a good agent for maintenance therapy after the acute control of seizures in adults with genetic generalized epilepsy or when the type of seizure/epilepsy syndrome is not clear.

- There is low- to moderate-quality evidence that the safety profile of levetiracetam was better than fosphenytoin, in terms of lesser cardiovascular adverse events.
- Sodium valproate has been associated with hepatic side-effects, in terms of raised transaminases and elevated ammonia levels. It is contraindicated in individuals with liver disease, which may not be evident when the person is brought in convulsing and needs emergency treatment.
- There is low-quality evidence that phenobarbital has a higher risk of respiratory depression and cardiovascular adverse effects as compared with sodium valproate.
- Phenobarbital and diazepam infusion carries the potential risk of sedation and respiratory depression, which may be increased if it is used after benzodiazepines.
- Phenytoin has associated risks of arrhythmia and hypotension and can be difficult to administer in adults with comorbid cardiac conditions.
- Most trials excluded women known to be pregnant. Seizures in pregnant women can be due to eclampsia which requires different treatment. Fosphenytoin or levetiracetam may be a better choice for women with epilepsy who have status epilepticus.
- The recommendation that sodium valproate is not recommended in women and girls of childbearing potential because of potential harm to the fetus, is not included in this question. Since this recommendation covers the short-term use of sodium valproate, the teratogenic effects may vary.

Research gaps

- Most of the evidence is from HICs. Further research is needed in LMICs.
- The studies had a small number of older adults. This is a special population group with several comorbid conditions and pharmacokinetics of medicines may be different in this age group.
- Post-trauma seizures may require special consideration – generally not included in studies.
- There is limited information on the proportion of electrographic seizures after resolution of clinical seizures in status epilepticus with different ASMs in children.
- As the outcome is highly dependent on the etiology of status epilepticus, trials in adults/children with status epilepticus of specific etiology such as infectious etiology (e.g. encephalitis) may be useful.

Implementation considerations

- The choice of medicine is affected by a number of factors, including availability, cost and side-effects.
- There are feasibility and affordability issues; intravenous fosphenytoin is not currently on the WHO EML (13).
- Adults treated for established status epilepticus require monitoring and may require ventilatory support; thus, secondary care is necessary.
- Delay in initiation and underdosing has been observed in treatment of status epilepticus. To terminate status epilepticus as quickly as possible drugs should be given in recommended dosages. There is a need to increase awareness of quick intervention, adequate initial benzodiazepine dosing and timely initiation of second-line treatment in benzodiazepine-resistant cases.
- Time to get medical attention is likely to be longer in LMICs, so advocacy is needed for better pre-hospital management of seizures.

EPI2. In children with established status epilepticus, i.e. seizures persisting after the first-line agent (benzodiazepine-resistant status epilepticus), which antiseizure medicines are associated with better clinical outcomes (stopping seizures and with less adverse effects)?

Recommendation (update):	In children with established status epilepticus, i.e. seizures persisting after two doses of benzodiazepines, intravenous fosphenytoin, intravenous phenytoin, intravenous levetiracetam, intravenous phenobarbital or intravenous valproic acid (sodium valproate) should be considered with appropriate monitoring. The choice of these medicines depends on local resources, including availability and facilities for monitoring.
Strength of recommendation:	Conditional
Certainty of evidence:	Moderate

Justification

- A new systematic review and meta-analysis was conducted to study comparisons between the ASMs for status epilepticus in children: Sharma et al., 2023 (12 RCTs).¹³ There is moderate- to high-quality evidence that there is no clinically important difference in efficacy between intravenous phenytoin, fosphenytoin, levetiracetam or sodium valproate for the treatment of benzodiazepine-resistant status epilepticus in children. There is low-quality evidence that phenobarbital may be more effective than phenytoin or sodium valproate in the treatment of benzodiazepine-resistant status epilepticus in children.
- Another factor of concern is the speed of administration. Fosphenytoin, levetiracetam and sodium valproate can be administered within 10 minutes, whereas phenytoin and phenobarbital need to be infused over 20 minutes. Time is of the essence while treating status epilepticus.
- There is low- to moderate-quality evidence that the safety profile of levetiracetam was better than fosphenytoin, phenytoin or sodium valproate in terms of less requirement for intubation, and lesser overall adverse effects.
- There is insufficient evidence to recommend the use of lacosamide or diazepam infusion at this time.

Remarks

- Status epilepticus is a medical emergency which can lead to profound systemic and neurological damage and is associated with significant short-term and long-term mortality. Timely control of status epilepticus is of paramount importance to improve the outcomes.
- A staged treatment protocol for management of status epilepticus is recommended.
 - Approximately 30–40% of all individuals fail to respond to initial treatment with benzodiazepines (benzodiazepine-resistant or established status epilepticus) and need further treatment with other intravenous ASM, i.e. established status epilepticus. The treatment of established status epilepticus is the focus of this recommendation with the above medicines initiated when seizures persist after two doses of benzodiazepines.
- Both levetiracetam and sodium valproate are broad spectrum drugs active against all types of seizures, and hence may be a good agent for maintenance therapy after the acute control of seizures in children with genetic generalized epilepsy or when the type of seizure/epilepsy syndrome is not clear. If available, intravenous levetiracetam should be considered because of its superior safety profile.

¹³ Sharma S, Jain P, Aneja S. Antiseizure medicine treatment for established status epilepticus in adults. 2023 (in preparation).

- There is low- to moderate-quality evidence that the safety profile of levetiracetam was better than fosphenytoin in terms of less requirement for intubation.
- There is low- to moderate-quality evidence that the safety profile of sodium valproate was better than phenytoin for cardiovascular adverse effects, and better than fosphenytoin in terms of less requirement for intubation.
- The advantages of sodium valproate include a smaller risk for cardiorespiratory side-effects.
- Sodium valproate has, however, been associated with risks for hepatotoxicity and pancreatitis. It is contraindicated in individuals with liver disease, which may not be evident when the person is brought in convulsing and needs emergency treatment. Also, sodium valproate is contraindicated in inherited metabolic – including mitochondrial – disorders, which may manifest in children with seizures and status epilepticus.
- Phenobarbital may cause sedation and respiratory depression, and the risk may be increased if it is used after benzodiazepines.
- Phenytoin is associated with risks for arrhythmia and hypotension, and it is difficult to administer in particular settings.
- The recommendation that sodium valproate is not recommended in women and girls of childbearing potential because of potential harm to the fetus, is not included in this question. Since this recommendation covers the short-term use of sodium valproate, the teratogenic effects may vary.

Research gaps

- Most of the research is from HICs. Further studies are needed in LMICs.
- Further research is needed on the proportion of electrographic seizures after resolution of clinical seizures in status epilepticus with different ASMs in children.
- As the outcome is highly dependent on the etiology of status epilepticus, trials in adults/children with status epilepticus of specific etiology, such as infectious etiology (e.g. encephalitis), may be useful to improve understanding.

Implementation considerations

- The choice of medicine is affected by a number of factors, including availability, cost and side-effects.
- There are feasibility and affordability issues; intravenous fosphenytoin is not currently on the *WHO model list of essential medicines for children* (EMLc) (132).
- Children treated for established status epilepticus require monitoring and may require ventilatory support; thus, tertiary/secondary care is necessary.
- Delay in initiation and underdosing has been observed in treatment of status epilepticus. To terminate status epilepticus as quickly as possible medicines should be given in recommended dosages. There is a need to increase awareness of quick intervention, adequate initial benzodiazepine dosing and timely initiation of second-line treatment in benzodiazepine-resistant cases.
- Time to get medical attention is likely to be longer in LMICs, so advocacy is needed for better pre-hospital management of seizures.

EPI3. For adults and children with epilepsy, which antiseizure medicines are effective and safe?

Recommendation (update):

3.1 Generalized onset seizures:

Monotherapy with lamotrigine or levetiracetam, or valproic acid (sodium valproate), should be offered as first-line treatment for generalized onset seizures in men/boys and women/girls who are not of childbearing potential.

In women and girls of childbearing potential with generalized onset seizures, lamotrigine or levetiracetam should be offered as first-line monotherapy.

If the first monotherapy is not successful for generalized onset seizures, an alternative first-line monotherapy should be tried.

Valproic acid (sodium valproate) is not recommended in women and girls of childbearing potential owing to the high risk of birth defects and neurodevelopmental disorders in children exposed to valproic acid (sodium valproate) in the womb.

If lamotrigine, levetiracetam and valproic acid (sodium valproate) are not available for generalized onset seizures, monotherapy with either phenytoin or phenobarbital can be considered.

Strength of recommendation:	Strong
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Certainty of evidence:	High
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3.2 Focal onset seizures:

Monotherapy with lamotrigine or levetiracetam should be offered as first-line treatment for focal onset seizures in children and adults with epilepsy.

If neither lamotrigine nor levetiracetam are available, then carbamazepine should be used as an alternate first-line treatment for focal onset seizures in children and adults with epilepsy.

If the first monotherapy is not successful for focal onset seizures, an alternative first-line monotherapy should be tried.

Lacosamide should be offered as a second-line monotherapy for focal onset seizures if none of the first-line medicines are effective.

If antiseizure medicine monotherapy is unsuccessful in people with generalized onset seizures or focal onset seizures, prompt referral should be made to a specialist for consideration of other treatment options.

Strength of recommendation:	Strong
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Certainty of evidence:	High
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Justification

- Evidence was extracted from one systematic review and NMA: Nevitt et al., 2022 (89 trials) (183).
- For generalized onset seizures there is high-certainty evidence to suggest that there is no statistically significant difference in time-to-seizure remission by ASM treatment (carbamazepine, lacosamide, lamotrigine, levetiracetam, phenobarbital, phenytoin, sodium valproate, topiramate).
- For generalized onset seizures there is high-certainty evidence to suggest that levetiracetam and lamotrigine perform significantly better than carbamazepine in terms of adverse events (HR = 0.56; 95% CI: 0.44 to 0.73 for lamotrigine versus carbamazepine, HR = 0.65; 95% CI: 0.47 to 0.90 for levetiracetam versus carbamazepine). Valproic acid also has an advantage over carbamazepine in terms of adverse events (HR = 1.96; 95% CI: 1.13 to 3.39).
- Given the risks associated with sodium valproate if prescribed to women and girls who are able to have children, lamotrigine or levetiracetam should be used as first-line treatment in this population.
- For focal onset seizures there is high-certainty evidence to suggest that carbamazepine performs better than gabapentin in terms of seizure remission (HR = 1.29; 95% CI: 1.06 to 1.57), and that carbamazepine has similar performance to other ASMs, including levetiracetam and lamotrigine.
- For focal onset seizures, levetiracetam and lamotrigine perform significantly better than carbamazepine in terms of adverse events (HR = 0.56; 95% CI: 0.44 to 0.73 for lamotrigine versus carbamazepine, HR = 0.65; 95% CI: 0.47 to 0.90 for levetiracetam vs carbamazepine). Given their better side-effect profile and similar efficacy to carbamazepine, lamotrigine and levetiracetam are now recommended for focal epilepsy.

Remarks

- As ASM choice depends on seizure semiology, outcomes are reported separately for focal onset seizures (focal seizures with or without awareness, focal to bilateral tonic-clonic seizures) and generalized onset tonic-clonic seizures (with or without other generalized seizure types such as myoclonus or absence seizures).
- All ASMs considered (carbamazepine, lamotrigine, oxcarbazepine, topiramate, gabapentin, sodium valproate, levetiracetam, lacosamide, zonisamide, phenytoin, phenobarbital) are effective in controlling seizures.
- Lamotrigine, topiramate, sodium valproate, levetiracetam, lacosamide, zonisamide and phenytoin are considered broad-spectrum ASMs effective against multiple seizure types. Carbamazepine and oxcarbazepine are ASMs mainly utilized for focal onset seizures. Carbamazepine and oxcarbazepine can be effective against generalized tonic-clonic seizures in people with generalized onset epilepsy, although they may exacerbate other seizure types in these individuals. Gabapentin is not an appropriate medicine in generalized epilepsy and should only be considered in those with focal onset seizures.
- No systematic review of RCTs comparing these ASMs with placebo was found. It is considered unethical to conduct RCTs comparing standard ASMs, especially as monotherapy, with placebo in established epilepsy as epilepsy should be treated to decrease morbidity and premature mortality.
- Both levetiracetam and sodium valproate are effective against all types of seizures, and hence may be ASMs of choice when the type of seizure/epilepsy syndrome is not clear.
- All ASMs are associated with adverse effects. Phenobarbital is associated with a higher risk of short- and long-term tolerability problems.
- When taken during pregnancy, sodium valproate is associated with a markedly higher risk of fetal malformations. Sodium valproate (valproic acid) has also been associated with hepatic side-effects, in terms of raised transaminases and elevated ammonia levels. Sodium valproate is contraindicated in individuals with liver disease.
- Phenytoin, despite being used as a first-line drug in some places, has a problematic pharmacokinetic profile. Phenytoin has associated risks of arrhythmia and hypotension and can be difficult to administer in adults with comorbid cardiac conditions.
- Most trials excluded women known to be pregnant. Seizures in pregnant women can be due to eclampsia, which requires different treatment strategies.

Research gaps

- Most of the evidence is from HICs. Further research is needed in LMICs.
- The evidence did not allow for consideration of adults and children/adolescents as subgroups. Further detail is required around adverse events in these subgroups.
- The studies had a small number of older adults. This is special population group with several comorbid conditions and pharmacokinetics of medicines may be different in this age group.
- No evidence was located on the important outcomes of mortality or quality of life.

Implementation considerations

- The choice of medicine is affected by a number of factors, including seizure semiology, comorbidities, availability, cost and side-effects.
- There are feasibility and affordability issues; lacosamide is not currently on the WHO EML (13) or the EMLc (132).
- Phenobarbital, being a controlled substance, faces strict regulations in many countries which affects its accessibility.

EPI4. What is the effectiveness and safety of antiseizure medicines in women of childbearing potential?

Recommendation (update):

4.1 The efficacy of antiseizure medicines (ASMs) is not thought to differ in males and females. As such, this recommendation builds on **EPI3** and focuses on the medicines that are now being preferentially recommended as therapeutic options.

In women and girls with epilepsy who are of childbearing potential, lamotrigine or levetiracetam should be offered as first-line monotherapy for both generalized onset seizures and focal onset seizures.

Women with epilepsy should have seizures controlled as well as possible with the minimum dose of ASMs taken in monotherapy, wherever possible.

Valproic acid (sodium valproate) is not recommended in women and girls of childbearing potential because of potential harm to the fetus.

Strength of recommendation:	Strong
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Certainty of evidence:	Very low
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4.2 Standard breastfeeding recommendations remain appropriate for women with epilepsy taking the ASMs included in this review (phenobarbital, phenytoin, valproic acid [sodium valproate], carbamazepine, lamotrigine, levetiracetam, topiramate, lacosamide).

Strength of recommendation:	Strong
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Certainty of evidence:	Very low
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Justification

- Evidence was extracted from one systematic review and NMA: Veroniki et al., 2017 (96 studies; 92 cohort studies, 3 case–control studies and 1 RCT) (184).
- Most ASMs are associated with higher risks of major congenital malformations in offspring of women taking these medicines during pregnancy compared with controls who were not taking an ASM.
- The highest risks of major (OR = 2.93; 95% CI: 2.36 to 3.69) and minor (OR = 17.76; 95% CI: 1.60 to 633.30) congenital malformation were reported in infants of women taking sodium valproate.
- Phenobarbital, phenytoin and carbamazepine were also associated with higher risks of major and minor congenital malformations.
- Topiramate was associated with higher risks of major congenital malformations with no information on minor congenital malformations available.
- The risk of major congenital malformation was not significantly higher in infants of women taking lamotrigine (OR = 0.96; 95% CI: 0.72 to 1.25) or levetiracetam (OR = 0.72; 95% CI: 0.43 to 1.16). No information on minor congenital malformations is available.
- There were no data on the teratogenic effect of lacosamide.
- There were no high-quality studies identified on the side-effects related to ASM exposure exclusively through breast-milk and the 2015 recommendation has been validated by the GDG.
- Due to the high risk of teratogenic effect with valproic acid, the GDG believed it was important to provide clear directions on the use of ASM in women and girls with epilepsy who are of childbearing potential and therefore made a strong recommendation despite the low certainty of evidence.

Remarks

- Major congenital malformations include malformations present from birth with surgical, medical, functional or cosmetic importance (cardiac malformations, cleft lip/palate, club foot, hypospadias, inguinal hernia, and undescended testes in boys). Minor congenital malformations include any congenital malformation that did not qualify as major congenital malformation.

Research gaps

- Most of the research is from HICs. Further research is needed in LMICs.
- There were no data on the side-effects related to ASM exposure exclusively through breast-milk. It is, though, noted that the amount of ASM in breast-milk is extremely low and that the baby will likely have been exposed to the same ASM(s) in higher concentration while in utero.

Implementation considerations

- The choice of medicine is affected by a number of factors, including seizure semiology, comorbidities, availability, cost and side-effects.
- Women and girls of childbearing potential who are prescribed sodium valproate should be advised to use effective contraception without interruption, for the entire duration of treatment. Further information on contraception is available in the WHO fact sheet on family planning and contraceptive methods (185). They must be provided with information on pregnancy prevention and risks associated with use of sodium valproate during pregnancy, and referred for contraceptive advice if they are not using effective contraception. When choosing the contraception method, individual circumstances should be evaluated in each case, involving the woman in the discussion to guarantee her engagement and compliance with the chosen measures.
- If a woman taking sodium valproate is planning to become pregnant, a person trained in the management of epilepsy in pregnant women should consider alternative treatment options. Women should be informed of the need to consult their physician as soon as they are planning pregnancy and to urgently consult their physician in case of pregnancy.
- Every effort should be made to switch from sodium valproate to appropriate alternative treatment prior to conception. If switching is not possible, the woman should receive further counselling regarding the risks of sodium valproate for the unborn child to support her informed decision-making.

- A specialist should periodically review whether sodium valproate is the most suitable treatment for all women of childbearing potential taking sodium valproate.
- ASM polytherapy is, in general, associated with higher risks of congenital malformations than ASM monotherapy.

EPI5. Which interventions are effective in preventing epilepsy-related mortality, including sudden unexpected death of someone with epilepsy (SUDEP)?

Recommendation (new):	Nocturnal supervision should be considered for prevention of sudden unexpected death in epilepsy (SUDEP).	
	Strength of recommendation:	Conditional
	Certainty of evidence:	Very low

Justification

- Evidence was extracted from one systematic review: Maguire et al., 2020 (1 case-control study) (186).
- Very low-certainty evidence suggests that supervision at night reduces the incidence of SUDEP (OR = 0.34; 95% CI: 0.22 to 0.53).
- SUDEP has a reported incidence of 1.2–1.3 per 1000 person-years and represents one of the most common causes of mortality in people with epilepsy (187,188).
- This conditional recommendation is made with very low-certainty evidence. As SUDEP is the most common epilepsy-related cause of death, nocturnal supervision offers a low-risk, low-cost intervention that merits consideration due to the balance of potential benefits and risks. Consideration of the following domains of the GRADE EtD framework contributed strongly to the decision to make a recommendation on this topic: values, health equity, equality and non-discrimination, human rights and sociocultural acceptability and feasibility.
- evidence of a seizure, excluding documented status epilepticus and in whom postmortem examination does not reveal a structural or toxicological cause for death.
- This intervention is considered especially appropriate for those who have convulsive seizures from sleep.
- Nocturnal supervision was defined by Langan et al. (2005) as “the presence of an individual of normal intelligence and at least 10 years old in the bedroom” (189). The use of special precautions is also considered as a part of nocturnal supervision in this recommendation. Special precautions involved regular checks throughout the night or the use of a listening device.
- There are limited anticipated risks of nocturnal supervision and this intervention is expected to be of low cost.

Research gaps

- The evidence presented is based on one study from a HIC. Further research is needed in LMICs.
- The evidence did not allow for consideration of adults and children/adolescents as subgroups. Further detail is required around specific considerations in these subgroups.

Remarks

- SUDEP is defined as sudden, unexpected, witnessed or unwitnessed, non-traumatic or non-drowning death of people with epilepsy, with or without

Implementation considerations

- Some training is required for the person performing checks, but this is anticipated to be minimal.
- All reasonable measures to reduce the risks of having seizures and to mitigate the risks from seizures should be initiated.
- People with epilepsy should be encouraged to adhere to their ASMs, to avoid sleep deprivation, to avoid excess alcohol consumption and to not take recreational substances. These measures will reduce the risk of having a seizure and thereby reduce the risk of seizure-associated mortality.
- People with epilepsy should also be informed to exercise due caution so that, were they to have a seizure, the chance of injury to themselves or others is minimized. People with epilepsy should not, for example, have baths, but shower or take strip-washes instead. People with epilepsy, especially those with seizures arising from sleep, should avoid sleeping prone to reduce the risk from sleep seizures.
- Physicians should identify comorbid mental health conditions and, if present, implement early effective interventions as they contribute to increased seizure risk and attendant risks, including SUDEP.

3.9 Overarching areas (OVE)



OVE1. Are psychosocial interventions (i.e. psychoeducation, cognitive-behavioural therapy, counselling, self-help groups) for carers of persons with schizophrenia/psychosis/schizophrenia spectrum disorder, bipolar disorder or substance use disorder effective compared with placebo/other controls?

Recommendation (new):	Psychosocial interventions – namely psychoeducation using problem-solving and cognitive-behavioural approaches (either individual or family-based), self-help interventions and mutual support groups – should be considered for carers of persons with psychosis or bipolar disorder.
	Strength of recommendation: Conditional
	Certainty of evidence: Moderate (carers of persons with psychosis or bipolar disorder), very low (carers of persons with substance use disorder)

Justification

- Evidence was extracted from a systematic review, Sampogna et al., 2023,¹⁴ which included:
 - 47 studies on carers of persons with schizophrenia/psychosis/schizophrenia spectrum disorder (34 RCTs, 8 pre–post design, 1 non-equivalent control group design, 4 with other designs);
 - 15 studies on carers of persons with bipolar disorder (12 RCTs, 3 pre–post design); and
 - 4 studies on carers of persons with substance use disorder (2 RCTs, 2 pre–post design).
- There is moderate-certainty evidence that a range of psychosocial interventions have a large effect in reducing caregiver burden in carers of persons with psychosis and bipolar disorder. When considered individually, psychoeducation, cognitive behavioural stress management and self-help interventions had a significant effect in carers of persons with psychosis and psychoeducation and family-led mutual support had a significant effect in carers of persons with bipolar disorder.
- There is moderate-certainty evidence that a range of psychosocial interventions have a moderate effect in improving quality of life/well-being in carers of persons with psychosis. When considered individually, psychoeducation had a significant effect in carers of persons with psychosis and psychoeducation and family-focused treatment had a significant effect in carers of persons with bipolar disorder.
- There is low-certainty evidence that a range of psychosocial interventions have a moderate positive effect on depressive symptoms in carers of persons with psychosis and bipolar disorder. When considered individually, psychoeducation had a significant effect in carers of persons with psychosis or bipolar disorder.
- The four available studies focusing on carers of persons with substance use disorder, half of which were of low quality, do not allow conclusions to be drawn about the effectiveness of psychosocial interventions in this population.
- None of the studies reported adverse outcomes or any harms identified as a result of any of the interventions.

¹⁴ Sampogna G, Brohan E, Luciano M, Chowdhary N, Fiorillo A. Psychosocial interventions for carers of people with severe mental and substance use disorders: a systematic review and meta analysis. 2023 Eur Psychiatry (in press).

Remarks

- Carers were defined as relatives or friends who provide informal and regular care/support to someone with severe mental illness.
- Interventions were included in the evidence review if they were provided to the carer alone or a family member (i.e. in the absence of the person with psychosis or bipolar disorder) and if they aimed to improve the carer's experience in terms of quality of life, personal burden (subjective/objective), depressive symptoms and/or well-being.
- The term “psychosocial intervention” is used loosely in research. Interventions are rarely manualized and often do not fall into mutually exclusive categories. The psychosocial interventions described feature common skills including problem-solving techniques, cognitive-behavioural techniques, teaching of coping strategies and communication skills.
- Psychoeducation refers to educational programmes with psychological or psychotherapeutic components that provide standardized information and focus on increasing carers' knowledge of the condition and developing specific coping skills to deal with caregiving challenges. They may be delivered individually or in group settings if the therapeutic components are adapted for delivery in a structured psychoeducational format (Cheng et al., 2020) (190).
- The choice of psychosocial intervention format largely depends on available resources in the health system as well as individual preferences.

Research gaps

- More research is required on the effectiveness of psychosocial interventions for carers of persons with substance use disorder.
- More research is needed in LMICs.

- The largest evidence base was for psychoeducation (13 out of 22 studies considered this in persons with psychosis; 6 out of 7 studies considered this in persons with bipolar disorder). Additional evidence on other psychosocial approaches is required.
- Evidence on whether the interventions improve outcomes for persons with psychosis, bipolar disorder or substance use disorders would help to understand if reducing caregiver burden and depression and increasing quality of life also has an impact on the well-being of the person that they care for.

Implementation considerations

- Psychosocial interventions can be delivered effectively in non-specialized health-care settings, as well as in other settings including specialized mental health care and social care.
- Integrating the provision of psychosocial interventions for carers into primary care provides many advantages, including more holistic support of carers as well as the person with schizophrenia/psychosis/schizophrenia spectrum disorder and bipolar disorder, opportunities for reducing the stigma of mental health problems and reduced costs.
- Face-to-face psychosocial interventions delivered by service providers is human resource-intensive as they require substantial provider time, training and supervision.
- Unguided psychosocial interventions can be delivered without any therapist/service provider support, so they can be less resource intensive and can be used in non-specialized health-care settings if there are insufficient human resources for face-to-face/guided psychosocial interventions.
- Country adaptation and translation of training materials and tools for the provision of psychosocial interventions is essential.

3.10 Psychosis and bipolar disorder (PSY)



PSY1. In adults with psychotic disorders (including schizophrenia) is antipsychotic medicine safe and effective?

Recommendation (update):	1.1 Oral antipsychotic medicines – namely aripiprazole, chlorpromazine, haloperidol, olanzapine, paliperidone, quetiapine, risperidone – should be offered for adults with a psychotic disorder (including schizophrenia), carefully balancing effectiveness, side-effects and individual preference.
	Strength of recommendation: Strong
	Certainty of evidence: Moderate
	1.2 Clozapine should be considered for adults with a treatment-resistant psychotic disorder (including schizophrenia) under mental health specialist supervision, carefully balancing effectiveness, side-effects and individual preference.
	Strength of recommendation: Conditional
	Certainty of evidence: Moderate

Justification

- Evidence was extracted from three systematic reviews: Ceraso et al., 2020 (75 RCTs on antipsychotic medicines in schizophrenia) (191); Leucht et al., 2017 (167 RCTs on antipsychotic medicines in schizophrenia) (192); and Schneider-Thoma et al., 2018 (596 RCTs on second-generation antipsychotic medicines in individuals with severe mental illness) (193).
- Antipsychotics showed moderate effects for overall efficacy (low-certainty evidence) and large effects for prevention of relapse (high-certainty evidence). Differences in efficacy between medicines were either small or uncertain.
- Overall, for the medicines with data available, social functioning (moderate-certainty evidence) and quality of life (very low-certainty evidence) were also improved.
- Antipsychotics were associated with various side-effects (very low- to low-certainty evidence) including movement disorders, weight gain, metabolic side-effects, prolactin increase, sexual side-effects, QT prolongation, sedation, which all appear in varying degrees. The propensity

to produce these side-effects differed between the agents, but the differences were overall less pronounced than the efficacy differences.

Remarks

- The medicines included in the recommendation correspond to the WHO EML (13) and are listed in alphabetical order.
- Clozapine should be offered for treatment-resistant psychosis, defined as psychosis that has not shown improvement after receiving treatment from two alternative antipsychotics with adequate dose and time. Clozapine should only be offered where lab tests are available to monitor white blood cell count, and under a mental health specialist supervision.
- Evidence regarding the safety and effectiveness of fluphenazine is mainly concerning the long-acting injectable formulations. Please refer to [PSY4](#) recommendations for further information.
- This recommendation does not suggest that only medicine should be offered, but medicine may be offered in combination with psychotherapy. Please refer to [PSY11](#) for further information.

Research gaps

- Data on first-generation antipsychotics with few exceptions such as haloperidol and chlorpromazine were very limited. As these medicines are of lower cost, further trials on some of them with relevant pharmacological properties would be warranted.

Implementation considerations

- People living with psychotic disorders should be involved in medicine choice in a supported decision-making process, without coercion and in line with human rights instruments.
- Treatment with antipsychotic medicines should be combined with psychosocial interventions (see other PICO questions in this module).
- Acquisition costs can differ substantially and also throughout the world. Recent antipsychotics may have currently higher costs than some older antipsychotics.
- Disruption in medicine supply (common in LMICs) may interfere with continuation of treatment.
- For the treatment of psychotic disorders, the WHO EML (13) includes the following oral medicines:
 - haloperidol (therapeutic alternative: chlorpromazine);
 - risperidone (therapeutic alternatives: aripiprazole, olanzapine, paliperidone, quetiapine);
 - complementary list: clozapine.

PSY2. In adults with a first psychotic episode (schizophrenia) with full remission, how long should antipsychotic medicine be continued after remission in order to allow for the best outcomes?

Recommendation (update):

Maintenance therapy with antipsychotic medicine for a minimum of 7–12 months should be offered in adults with a first episode of psychosis (including schizophrenia) in remission, carefully balancing effectiveness, side-effects and individual preference.

Strength of recommendation: Strong

Certainty of evidence: Moderate

Justification

- Evidence was extracted from three systematic reviews: Ceraso et al., 2020 (75 RCTs on maintenance treatment with antipsychotic medicines in schizophrenia) (191); Kishi et al. 2019 (10 RCTs on discontinuation versus maintenance of antipsychotic medicines in schizophrenia) (194); and Schneider-Thoma et al., 2018 (596 RCTs on second-generation antipsychotic medicines and short-term somatic serious adverse events in individuals with severe mental illness) (193).
- Maintenance therapy was significantly superior to discontinuation with a follow-up of up to 12 months as well as up to 24 months. However, antipsychotics were associated with side-effects.

- The certainty of evidence was high for relapse at 12 and 24 months and low for leaving the study early due to adverse events.

Remarks

- Discontinuation of antipsychotics should always be done by gradually and slowly reducing the medicine dose. When medicines are discontinued, people living with schizophrenia and family members need to be educated to detect the re-emergence of symptoms early to allow for close clinical monitoring of relapse.

Research gaps

- Most of the evidence is from HICs. Further research is needed in LMICs.
- There was no evidence for maintenance therapy for more than two years and evidence was scarce between one- and two-year follow-up. More studies are required on longer term maintenance.
- More studies applying gradual tapering of the antipsychotic in the placebo group are needed.

Implementation considerations

- As individuals with a first psychotic episode usually respond well to antipsychotics, drug choice should be mainly based on side-effect profiles.
- People living with schizophrenia should be involved in drug choice in a supported decision-making process.
- Treatment with antipsychotic medicines should be combined with psychosocial interventions (see other PICO questions in this module).
- Acquisition costs can differ substantially. Also, throughout the world, second-generation and other

newer antipsychotics may have higher costs than older first-generation antipsychotics.

- Interruptions in medicine availability (common in LMICs and in supply chain interruption such as during emergencies) may interfere with continuation of treatment. Reliability of supply should inform choice of medicine.
- For the treatment of psychotic disorders, the WHO EML (13) includes:
 - fluphenazine (therapeutic alternatives: haloperidol decanolate, zuclopenthixol decanolate);
 - haloperidol (therapeutic alternative: chlorpromazine);
 - haloperidol injection;
 - olanzapine;
 - paliperidone (therapeutic alternative: risperidone injection);
 - risperidone (therapeutic alternatives: aripiprazole, olanzapine, paliperidone, quetiapine);
 - complementary list: clozapine.

PSY3. In adults with bipolar disorder in remission, how long should antipsychotic medicine or mood stabilizers be continued after remission in order to allow for the best outcomes?

Recommendation (update):	Maintenance therapy with mood stabilizers or antipsychotic medicines should be considered for at least six months for adults with bipolar disorder in remission, carefully balancing effectiveness, side-effects and individual preference.	
	Strength of recommendation:	Conditional
	Certainty of evidence:	Low

Justification

- Evidence was extracted from three systematic reviews: Kishi et al., 2021 (22 RCTs comparing between antipsychotic/mood stabilizer discontinuation and maintenance groups in individuals with bipolar disorder) (195); Kishi et al., 2021 (41 RCTs on antipsychotics and/or mood stabilizers for individuals with bipolar disorder in the maintenance phase) (196); and Schneider-

Thoma et al., 2018 (596 RCTs on second-generation antipsychotic medicines and short-term mortality in individuals with severe mental illness) (193).

- The anticipated desirable effects for maintenance therapy are moderate to large for recurrence rate of any mood episode/depressive episode/manic, hypomanic or mixed episode at different time points. Most data were available for a follow-up of up to six months.

- There is a moderate-to-large increase of adverse effects (discontinuation due to adverse effects) depending on the medicine used.
- The certainty of evidence was moderate for the outcome recurrence. The certainty of evidence was very low to low for the outcome adverse effects.

Remarks

- This recommendation refers to people living with bipolar disorder in the maintenance phase, characterized by the absence of acute symptoms.
- The use of lithium should be considered as first-line of treatment for bipolar disorder only if clinical and laboratory monitoring are available and should only be prescribed under mental health specialist supervision. If laboratory examinations are not available or feasible, lithium should be avoided and other mood stabilizers or antipsychotics should be considered. Do not prescribe lithium where the lithium supply may be frequently interrupted due to increased risk of relapse. Clinicians should conduct kidney and thyroid function, complete blood count, electrocardiogram (ECG) and pregnancy tests before beginning treatment where possible.
- Sodium valproate should not be used in women and girls of childbearing potential because of the high risk of birth defects and neurodevelopmental disorders in children exposed to sodium valproate in utero (see recommendation [PSY8.2](#)).

- Polytherapy should be avoided as a treatment option when commencing maintenance therapy.

Research gaps

- There is limited evidence on how long antipsychotic medicine or mood stabilizers should be continued after remission for first episode bipolar disorder.
- Most of the evidence is from HICs. Further research is needed in LMICs.

Implementation considerations

- People living with bipolar disorder should be involved in medicine choice in a supported decision-making process.
- Treatment with antipsychotic medicines or mood stabilizers should be combined with psychosocial interventions (see other recommendations in this module).
- Acquisition costs can differ substantially and also throughout the world. Recent antipsychotics may have higher costs than older antipsychotics.
- Discontinuities in medicine availability (common in LMICs) may interfere with the continuation of treatment.
- Lithium carbonate, carbamazepine and quetiapine (therapeutic alternatives: aripiprazole, olanzapine, paliperidone) are available in the WHO EML (13).

PSY4. In adults with psychotic disorders (including schizophrenia) requiring long-term treatment, what is the safety and role of depot antipsychotic medicine?

Recommendation (update):

Long-acting injection (LAI) antipsychotic medicines – namely fluphenazine, haloperidol, paliperidone, risperidone and zuclopenthixol – should be considered as an alternative to oral antipsychotic medicines for adults with psychotic disorders (including schizophrenia) requiring long-term treatment, carefully balancing effectiveness, side-effects and individual preference.

Strength of recommendation: Conditional

Certainty of evidence: Moderate

Justification

- Evidence was extracted from two systematic reviews: Kishimoto et al., 2021 (32 RCTs, 65 cohort studies, and 40 pre–post studies on long-acting injectable (LAI) versus oral antipsychotics for the maintenance treatment of schizophrenia) (197); Schneider-Thoma et al., 2022 (132 RCTs on comparative efficacy and tolerability of 32 oral and LAI antipsychotics for the maintenance treatment of adults with schizophrenia) (198).
- Almost all LAIs compared with placebo had large effects for relapse prevention. Clopenthixol LAI was not statistically significant compared with placebo, but did outperform placebo in pairwise meta-analysis. In summary, there was not much difference between the several LAIs compared with placebo for relapse prevention; they all showed large efficacy.
- The results for overall symptoms and overall functioning were similar to those for the outcome relapse (i.e. superiority of most LAIs over placebo; no clear evidence of differences between antipsychotics), but data were sparse.
- All LAIs showed less discontinuation for any reason compared with placebo.
 - Sedation: Olanzapine LAI, paliperidone LAI, haloperidol LAI and aripiprazole LAI increased the risk for sedation compared with placebo in various degrees; the 95% CIs indicated no significant effect.
 - Use of anticholinergic medicine: All LAIs were associated with the use of anticholinergic medicine.

- Tardive dyskinesia: Tardive dyskinesia was a rare event in the identified studies and results were uncertain, so differences could not be identified between the interventions.
- QT interval: There were no significant results.
- Body weight: Paliperidone LAI seemed to increase body weight, aripiprazole LAI did not.
- Prolactin: Paliperidone LAI seemed to increase prolactin, aripiprazole LAI did not.

Remarks

- The medicines included in the recommendation correspond to the WHO EML (13), including both those that are currently included or being considered for addition. The above recommendation is based on the context, availability and costs of using LAIs.

Research gaps

- Most of the evidence is from HICs.
- More trials comparing second-generation LAI antipsychotics head-to-head are needed.
- More trials comparing first-generation antipsychotics and second-generation antipsychotics are needed.

Implementation considerations

- With LAIs, compliance of people living with psychotic disorders with treatment plans can be improved.
- Acquisition costs of LAIs can differ substantially and also throughout the world.
- People living with long term psychotic disorders should be involved in medicine choice in a

supported decision-making process, without coercion and in line with human rights instruments.

- Treatment with antipsychotic medicines should be combined with psychosocial interventions (see other recommendations in this module – namely [PSY11](#)).

- The dosing interval should be considered based on the LAIs prescribed and their recommended intervals. For further information on duration of treatment, please refer to recommendation [PSY2](#).

PSY5. Is antipsychotic medicine effective and safe for adolescents with psychotic disorders (including schizophrenia)?

Recommendation (update):

5.1 Oral antipsychotic medicines – namely aripiprazole, olanzapine, paliperidone, quetiapine, risperidone – should be considered under specialist supervision for adolescents with psychotic disorders (including schizophrenia), carefully balancing effectiveness, side-effects and individual preference.

Strength of recommendation: Conditional

Certainty of evidence: Low

5.2 Clozapine should be considered for adolescents with a treatment-resistant psychotic disorder (including schizophrenia) under specialist supervision, carefully balancing effectiveness, side-effects and individual preference.

Strength of recommendation: Conditional

Certainty of evidence: Low

Justification

- Data were extracted from an NMA on efficacy, acceptability and tolerability of antipsychotics in children and adolescents with schizophrenia: Krause et al., 2018 (28 RCTs) (199).
- Few antipsychotics have been tested in children and adolescents. The medicines mentioned above were the only efficacious ones.
- With regard to overall change in symptoms, all investigated medicines for which evidence in this age group was available were significantly superior to placebo (clozapine, olanzapine, molindone, risperidone, lurasidone, aripiprazole, quetiapine, paliperidone, asenapine) with the exception of haloperidol, trifluoperazine, loxapine, ziprasidone and fluphenazine. Clozapine ranked as the most efficacious medicine with large effects.
- Clozapine was followed by (compared with placebo) olanzapine, molindone, risperidone, lurasidone, aripiprazole, quetiapine, paliperidone and asenapine. Overall, effect sizes were moderate to large.
- For quality of life, quetiapine and lurasidone were significantly superior to placebo with small effects.
- For social functioning, risperidone, aripiprazole and lurasidone were significantly superior to placebo with small-to-moderate effects.
- For weight gain, molindone produced a weight decrease compared with the placebo, yet not significantly. Lurasidone was rather weight-neutral with no significant results. Aripiprazole, asenapine, risperidone, paliperidone and olanzapine produced significantly more weight gain than placebo with a small effect for aripiprazole, moderate effect sizes

for asenapine and risperidone and large effects for paliperidone, clozapine, quetiapine and olanzapine.

- Most weight gain was produced by clozapine, quetiapine and olanzapine.
- For prolactin increase, aripiprazole and asenapine showed the lowest prolactin increase. Quetiapine, paliperidone, olanzapine, haloperidol and risperidone showed significantly higher prolactin increase than placebo. Risperidone and haloperidol showed the largest prolactin increase compared with the placebo.
- Concerning the outcome sedation, most medicines produced this outcome. Risperidone, aripiprazole, haloperidol, olanzapine, loxapine, paliperidone, asenapine and clozapine led to significantly more sedation than placebo.
- The use of anticholinergic medicine was significantly higher for paliperidone compared with placebo.

Remarks

- The medicines included in the recommendation correspond to the WHO EML (13) and are listed in alphabetical order.
- Clozapine should only be offered where lab tests are available to monitor white blood cell count, and under a mental health specialist's supervision.

Research gaps

- Insufficient knowledge of long-term side-effects in adolescents.

Implementation considerations

- Only a few antipsychotics are officially licensed for children and adolescents which should be considered in medicine choice, taking into account the country and context.
- Antipsychotic medicine should be considered for adolescents with psychotic disorders only under supervision of a mental health specialist.
- Adolescents are more susceptible to side-effects from antipsychotic medicines than adults. In turn, during the clinical decision-making process, adolescents living with psychosis should be made aware of benefits and side-effects so that they are able to make informed choices regarding the treatment plan. Additionally, carer preference should be taken into consideration.
- Furthermore, given the higher susceptibility of adolescents to side-effects, the medicines approved in a given country should be carefully considered before formulating a treatment plan.

PSY6. Is psychotropic medicine effective and safe for adolescents with bipolar disorder?

Recommendation (update):

Psychotropic medicines (antipsychotic medicines, namely aripiprazole, olanzapine, quetiapine, risperidone; and mood stabilizers, namely lithium) should be considered under specialist supervision for adolescents with bipolar disorder (current episode manic), carefully balancing effectiveness, side-effects and individual preference.

Strength of recommendation: Conditional

Certainty of evidence: Very low

Justification

- Evidence was extracted from two systematic reviews: DelBello et al., 2022 (4 RCTs in an NMA of efficacy and safety of second-generation antipsychotic medicines in youths with bipolar depression) (200); and Ciray et al., 2020 (11 placebo-controlled pharmacological

trials in children and adolescents with bipolar disorder manic episode) (201).

- Few antipsychotics/mood stabilizers have been tested in children and adolescents. The medicines mentioned above were the only efficacious ones.

- The systematic review on bipolar depression in adolescents (DelBello et al., 2022) only identified studies for lurasidone, quetiapine, olanzapine–fluoxetine combination. Systematic reviews about classical mood stabilizers and antidepressants were not identified. Lurasidone and olanzapine–fluoxetine combination significantly improved depressive symptoms, while quetiapine did not. Olanzapine–fluoxetine combination showed more discontinuation due to adverse effects than placebo (OR = 3.31; 95% CI: 1.08 to 8.75). Lurasidone was similar to placebo and quetiapine showed significantly fewer discontinuations than placebo. In this review, olanzapine caused most weight gain (not summarized in the evidence profile).
- The search process identified one systematic review on acute bipolar mania in children and adolescents, Ciray et al., 2020 (11 RCTs, 1974 participants), that compared different medicines with placebo. Effect sizes by pooling all medicines were moderate (SMD = -0.61; 95% CI: -0.78 to -0.44). The certainty of evidence was moderate. In the single studies, almost all investigated medicines were superior to placebo (topiramate, olanzapine, risperidone, aripiprazole, ziprasidone, quetiapine, asenapine, lithium). The most efficacious medicine was risperidone. As expected, there were side-effects such as weight-gain, prolactin increase, higher fasting glucose, etc.
- Children and adolescents are a particularly vulnerable group. Given the very limited evidence and known side-effects of antipsychotics from systematic reviews in adults, antipsychotic

medicines should only be given in a case-by-case manner by a specialist carefully balancing efficacy and side-effects.

Remarks

- There is not enough evidence to recommend the use of psychotropic medicine in adolescents with bipolar disorder (current episode depression). Preliminary evidence suggests that olanzapine–fluoxetine combination (very low certainty) and lurasidone (high certainty) are effective in reducing bipolar symptoms in adolescents with bipolar disorder (current episode depression).

Research gaps

- Randomized controlled trials are needed, particularly comparing pharmacological interventions with placebo and with each other, in children and adolescents with bipolar disorder in order to better know their efficacy and safety in this vulnerable group.
- Further high-quality evidence is required to understand the use of psychotropic medicines for adolescents requiring maintenance treatment.
- Ciray et al., 2020 investigated no side-effects. More research is needed to investigate side-effects of medicines in this age group (201).

Implementation considerations

- Adolescents living with bipolar disorder should be involved in medicine choice in a supported decision-making process.

PSY7. In adults with bipolar disorder (current episode mania), are antipsychotic medicines and mood stabilizers effective and safe?

Recommendation (update):

7.1 Oral antipsychotic medicines (namely aripiprazole, haloperidol, olanzapine, paliperidone or quetiapine) or mood stabilizers (namely carbamazepine, lithium, valproic acid [sodium valproate]) should be offered to adults with bipolar disorder (current episode mania), carefully balancing effectiveness, side-effects and individual preference.

Strength of recommendation:	Strong
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Certainty of evidence:	Low
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7.2 Valproic acid (sodium valproate) should not be used in women and girls of childbearing potential owing to the high risk of birth defects and neurodevelopmental disorders in babies in utero.

Strength of recommendation:	Strong
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Certainty of evidence:	Low
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Justification

- Data were extracted from an NMA: Kishi et al., 2022 (included 72 RCTs on pharmacological treatment for bipolar mania) (202).
- In the review, the antipsychotics aripiprazole, asenapine, cariprazine, haloperidol, olanzapine, paliperidone, quetiapine, risperidone and ziprasidone and the mood stabilizers carbamazepine, lithium and sodium valproate outperformed placebo significantly for the outcome response to treatment. The effect sizes were small to moderate.
- The review used for this PICO question only addressed the global tolerability outcome, “discontinuation due to adverse effects”. With regard to the outcome discontinuation due to adverse effects, the antipsychotics asenapine and haloperidol and the mood stabilizer lithium had significantly higher discontinuation rates than placebo. Effect sizes were small to moderate. No review that addressed specific side-effects of single agents was identified. The side-effects of various antipsychotics are well known from reviews in schizophrenia (see recommendation [PSY1](#)), among others, movement disorders, weight gain, metabolic side-effects, prolactin increase, sexual side-effects, QT prolongation, sedation, which all appear in varying degrees.
- According to the systematic review used, the mood stabilizers which were effective – carbamazepine, sodium valproate and lithium – have important side-effects as well. Rare, but extremely serious side-effects are that carbamazepine is associated with the risk of Stevens-Johnson syndrome and toxic epidermal necrolysis (203).
- An important side-effect of sodium valproate is its teratogenic potential. It significantly increases the risk of malformations such as neural tube defects and cleft palate at birth (204). The European Medical Agency (EMA) recommends avoiding sodium valproate in pregnancy and that it should not be used in the absence of pregnancy prevention programmes. For mania, teratogenicity is problematic as the condition leads to impaired judgement and an increase in risky promiscuous behaviour (205).
- Lithium has a very narrow therapeutic window beyond which it is toxic. It is associated with hypothyroidism, weight gain, eventually renal dysfunction and others, and it requires regular checking of blood levels.

- It should be noted that tamoxifen turned out to be highly effective in the systematic review used. However, it was only based on two small trials with very few participants and it does not have an official indication. Tamoxifen has serious side-effects such as uterine malignancy, thromboembolic events and embryo-fetal toxicity (206).
- Due to the public health importance of this topic, the strength of recommendation was judged as strong despite low-quality evidence. During manic episodes, bipolar disorder is a debilitating condition that may lead to an increased risk of mortality and, in turn, not having available treatment can pose serious risks to the person.

Remarks

- The use of lithium should be considered as first-line of treatment for bipolar disorder only if clinical and laboratory monitoring are available. Lithium should only be prescribed under mental health specialist supervision. If laboratory examinations are not available or feasible, lithium should be avoided and other mood stabilizers or antipsychotics should be considered. Do not prescribe lithium where the lithium supply may be frequently interrupted due to increased risk of relapse. Clinicians should conduct kidney and thyroid function, complete blood count, ECG and pregnancy tests before beginning treatment where possible.
- Sodium valproate should not be used in women and girls of childbearing potential because of the high risk of birth defects and neurodevelopmental disorders in children exposed to sodium valproate in utero (see recommendation [PSY8.2](#)).

Research gaps

- Most of the evidence is from HICs. Further research is needed in LMICs.
- Further research identifying specific side-effects of single agents is needed.

Implementation considerations

- People living with psychotic disorders should be involved in medicine choice in a supported decision-making process.
- Treatment with antipsychotic medicines/mood stabilizers should be combined with psychosocial interventions (see other recommendations in this module).
- Acquisition costs can differ substantially and also throughout the world. Recent antipsychotics may have higher costs than older antipsychotics.
- Lithium carbonate, sodium valproate (valproic acid), carbamazepine and quetiapine (therapeutic alternatives: aripiprazole, olanzapine, paliperidone) are available in the WHO EML (13).

PSY8. In adults with bipolar disorders in remission, are mood stabilizers and antipsychotics effective and safe?

Recommendation (update):

8.1 Mood stabilizers (namely carbamazepine, lithium, valproic acid [sodium valproate]) or oral antipsychotic medicines (namely aripiprazole, olanzapine, quetiapine) should be considered for maintenance treatment for adults with bipolar disorder in remission, carefully balancing effectiveness, side-effects and individual preference.

Strength of recommendation:	Conditional
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Certainty of evidence:	Low
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8.2 Valproic acid (sodium valproate) should not be used in women and girls of childbearing potential with bipolar disorder in remission owing to the high risk of birth defects and neurodevelopmental disorders in babies in utero.

Strength of recommendation:	Strong
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Certainty of evidence:	Low
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Justification

- Data were extracted from an NMA: Kishi et al., 2021 (41 RCTs on the use of mood stabilizers and/or antipsychotics for bipolar disorder in the maintenance phase) (196).
- Recurrence/relapse rate of any mood episode:*
 - For this outcome, almost all medicines reduced relapse: asenapine, aripiprazole plus sodium valproate, lithium plus oxcarbazepine, olanzapine, lithium plus sodium valproate, aripiprazole plus lamotrigine, aripiprazole once monthly, quetiapine, lithium, risperidone LAI, sodium valproate and lamotrigine all outperformed placebo.
 - Asenapine ranked first, aripiprazole plus sodium valproate ranked second and lithium plus oxcarbazepine ranked third in terms of recurrent/relapse.
 - The certainty of the evidence was low to moderate.
- Recurrence/relapse of depressive episodes:*
 - Aripiprazole plus sodium valproate, lamotrigine, lamotrigine plus sodium valproate, lithium, olanzapine, and quetiapine outperformed placebo for recurrence/relapse rate of depressive episodes.
 - Aripiprazole plus sodium valproate ranked first, lamotrigine plus sodium valproate ranked second and quetiapine ranked third.
 - The certainty of the evidence was very low to low.
- Recurrence/relapse of manic/hypomanic/ mixed episodes:*
 - For this outcome all medicines outperformed placebo except aripiprazole plus sodium valproate, carbamazepine, lamotrigine, and lamotrigine plus sodium valproate.
 - Asenapine ranked first, aripiprazole once monthly ranked second and lithium plus oxcarbazepine ranked third.
 - The certainty of the evidence was very low to moderate.
- Adverse effects:*
 - With regard to the outcome “discontinuation due to adverse effects”, lithium plus sodium valproate had significantly higher discontinuation rates than placebo.
 - Only asenapine showed a lower discontinuation rate than placebo.
- Due to the high risk of teratogenic effect with sodium valproate, the GDG believed it was important to provide clear directions on the use of sodium valproate in women and girls with bipolar disorder

in remission who are of childbearing potential and therefore made a strong recommendation despite the low certainty of evidence.

Remarks

- Remission is considered when there is absence of or minimal symptoms for several weeks. Remission, defined as the absence of or minimal symptoms for several weeks, was not necessarily an inclusion criteria in the trials included in the reviews.
- Maintenance therapy was used in the recommendation to define continuation of treatment with a lack of acute symptoms.
- Maintenance treatment should only be offered in primary health care settings where clinical supervision is able to be provided by a mental health specialist.
- In situations where one of the listed second-generation antipsychotics are not a feasible option for treatment, first-generation antipsychotics, namely chlorpromazine or haloperidol, may be considered for maintenance treatment for adults living with bipolar disorder.
- The use of lithium should be considered as first-line of treatment for bipolar disorder only if clinical and laboratory monitoring are available. Lithium should only be prescribed under mental health specialist supervision. If laboratory examinations are not available or feasible, lithium should be avoided and other mood stabilizers or antipsychotics should be considered. Do not prescribe lithium where the lithium supply may be frequently interrupted due to increased risk of relapse. Clinicians should conduct

kidney and thyroid function, complete blood count, ECG and pregnancy tests before beginning treatment where possible.

Research gaps

- Most of the evidence is from HICs. Further research is needed in LMICs.
- Further research is needed to consider the side-effects related to exposure to sodium valproate exclusively through breast-milk. It is, though, noted that the amount of sodium valproate in breast-milk is extremely low and that the baby will likely have been exposed to the same medicine in higher concentration while in utero.

Implementation considerations

- People living with bipolar disorder should be involved in medicine choice in a supported decision-making process.
- Treatment with antipsychotic medicines/mood stabilizers should be combined with psychosocial interventions (see other PICO questions in this module).
- Acquisition costs can differ substantially and also throughout the world. Recent antipsychotics may have higher costs than older antipsychotics.
- Lithium, sodium valproate and carbamazepine require regular blood monitoring, which also adds costs.
- Lithium carbonate, sodium valproate (valproic acid), carbamazepine and quetiapine (therapeutic alternatives: aripiprazole, olanzapine, paliperidone) are available in the WHO EML (13).

PSY9. In adults presenting with a depressive episode in bipolar disorder, are medicines with antidepressant effects (adjunct to maintenance treatment) effective and safe?

Recommendation (update):	<p>Fluoxetine, olanzapine, quetiapine, valproic acid (sodium valproate) or venlafaxine should be considered for adults with bipolar depression. If fluoxetine or venlafaxine are chosen, they should be co-administered with a mood stabilizer (namely quetiapine, olanzapine, carbamazepine, valproic acid [sodium valproate], lithium).</p>
Strength of recommendation:	Conditional
Certainty of evidence:	Very low

Justification

- Data were extracted from an NMA: Yildiz et al., 2023 (101 RCTs on pharmacotherapy for adults with bipolar depression) (207).
- The study showed small effects for reduction of depressive symptoms for the combination of olanzapine plus fluoxetine with moderate certainty of evidence (SMD = 0.41). Venlafaxine showed small effects as well (SMD = 0.47) with low certainty of evidence. Fluoxetine showed large effects (SMD = 0.75), based however on very low certainty of evidence.
- The other investigated (adjunctive) psychotropic medicines with antidepressant use (including antidepressants, mood stabilizers and antipsychotics), namely sertraline, paroxetine, imipramine, aripiprazole plus citalopram, sertraline plus lithium, bupropion, citalopram and risperidone plus paroxetine were not convincingly different than placebo. However, sertraline was also close to being possibly superior to placebo.
- Overall, data suggest that antidepressants (alone) may be efficacious with small effects, but it is unclear if they differ.
- For the outcome “manic switch”, all investigated medicines were not convincingly different than placebo. However, these data were mainly from short-term studies. Generally, manic switch seems to be a rare complication.

Remarks

- Please refer to recommendation [PSY8](#) to find further information on the recommendations for mood stabilizer and antipsychotic use in maintenance treatment.

Research gaps

- Most of the evidence is from HICs. Further research is needed in LMICs.
- Most of the available data are for antipsychotics; more data are needed on antidepressants.

Implementation considerations

- People living with bipolar disorders should be involved in medicine choice in a supported decision-making process.
- Acquisition costs can differ substantially and also throughout the world.
- Lithium carbonate, sodium valproate (valproic acid), carbamazepine and quetiapine (therapeutic alternatives: aripiprazole, olanzapine, paliperidone) are available in the WHO EML (13).
- Antidepressant treatment should begin at a low dose and be increased gradually if necessary.
- Individuals should be monitored carefully for early signs of manic symptoms. Antidepressants should be stopped soon after remission of depressive symptoms, while mood stabilizer should be continued.

PSY10. In adults with psychotic disorders (including schizophrenia), are psychological interventions (such as psychoeducation, family interventions and cognitive behavioural therapy) effective in the acute phase?

Recommendation (update):	Treatment based on cognitive behavioural therapy (CBT) should be considered for adults with psychotic disorders (including schizophrenia) in the acute phase of the condition where sufficient specialist support is available.	
	Strength of recommendation:	Conditional
	Certainty of evidence:	Moderate

Justification

- Data were extracted from an NMA: Bighelli et al., 2018 (53 RCTs on the use of seven psychological interventions to reduce positive symptoms in schizophrenia) (208).
- CBT was significantly superior to treatment as usual (TAU) for the outcome “overall symptoms”. The other interventions (hallucination focused integrative treatment [HFIT], experience focused counselling [EFC], acceptance and commitment therapy [ACT], metacognitive training [MT], mindfulness-based interventions [MF] – see below for definitions of interventions) were non-significant but showed small-to-medium effects compared with TAU.
- For the outcomes of “quality of life” and “functioning”, CBT was significantly superior to TAU. The other interventions showed small-to-medium non-significant effects.
- The certainty of evidence was moderate for CBT for overall symptoms and very low to low for the other interventions.
- The certainty of the evidence for the other outcomes was very low to low.

Remarks

- *Cognitive behavioural therapy (CBT)*: CBT for psychosis is usually based on an individualized case formulation and the establishment of collaborative goals with the people living with psychosis. Therapy components include the improvement of existing coping strategies, the development and practice of new ones, the modification of delusional beliefs

and beliefs about hallucinations and the challenge of dysfunctional schemas. Adaptive views of self are strengthened, including the re-evaluation of negative beliefs about the self.

- *Acceptance and commitment therapy (ACT)*: A manualized third-generation behavioural therapy that incorporates acceptance and mindfulness-based strategies to help people in overcoming negative thoughts and feelings.
- *Metacognitive training (MT)*: A group intervention whose aim is to make individuals aware of their cognitive biases by helping them to reflect on various cognitive biases and their role in the formation and maintenance of psychopathology. These individuals are then encouraged to discuss these biases and their implications with the help of real-life examples and practical exercises. It is presumed that when the individuals gain insight into their biases and relationship with psychopathology, they will challenge their beliefs and, thus, avoid the automatic cognitive traps.
- *Mindfulness-based interventions (MF)*: The intervention consists of guided meditation followed by reflective group discussion aimed at facilitating understanding, or metacognitive insight. During meditation, participants bring full awareness to difficult voices, feelings, thoughts and images, and also become aware of habitual coping reactions, safety behaviours and their effects. In meditation they practice letting go of these reactions and learn to observe and allow psychotic experiences to come and go without reacting. Meditation and

discussion lead to insight that struggling, judging and ruminating on psychotic experience creates distress, while mindful observation and acceptance of psychotic experience is empowering and calming.

- *Hallucination focused integrative treatment (HFIT)*: This treatment integrates motivational interventions, training in coping skills, CBT, operant conditioning and single-family therapy with medicine, psychoeducation and rehabilitation.
- *Experience focused counselling (EFC)*: EFC aims to make sense of the voice-hearing experience within the person's life context and supporting the person in learning to better deal with the experience as part of a recovery process. The intervention attempts to answer who and what problems the voices represent, also by uncovering traumatic life connections to voices.
- Integrating the provision of psychological interventions into primary care provision and other general and social care facilities has many advantages, including more holistic health care, increased accessibility for people in need of mental health care, opportunities for reducing the stigma of mental health problems and reduced costs.

Research gaps

- Most of the research is from HICs and, in general, psychological interventions have been developed in HICs. Further research is needed in LMICs.

- Many interventions other than CBT have so far been investigated in only a few trials and further study is required to understand whether the balance of effects differs by type of psychosocial intervention.
- Further research is needed on psychoeducation or family interventions focused on individuals in the acute phase of the disease.

Implementation considerations

- CBT requires specific training which may not be available in all LMICs.
- Differences in mental health infrastructure and resources should be considered.
- Variations in cultural context should be considered. There may be acceptability issues.
- Country adaptation and translation of training materials and tools for the provision of psychological interventions is essential.
- Face-to-face psychological interventions delivered by service providers is human resource-intensive as they require substantial provider time, training and supervision.
- For the safe implementation of psychological interventions among people with psychosis by non-specialized professionals, supervision by a mental health specialist is an important aspect that should be considered and planned prior to commencement (209).

PSY11. In adults with psychotic disorders (including schizophrenia), are psychological interventions (such as psychoeducation, family interventions and CBT) effective in the maintenance phase?

Recommendation (update):

Psychosocial interventions – namely family interventions, family psychoeducation, psychoeducation and cognitive behavioural therapy (CBT) – should be offered to adults with psychosis (including schizophrenia) during the maintenance phase, either alone or in combination.

Strength of recommendation: Strong

Certainty of evidence: Moderate

Justification

- Data were extracted from an NMA: Bighelli et al., 2021 (72 RCTs on the use of psychosocial and psychological interventions for relapse prevention in schizophrenia) (210).
- Most of the psychological interventions were significantly superior to TAU for relapse prevention. CBT, family intervention and relapse prevention programmes showed large effects.
- Family psychoeducation, integrated intervention and psychoeducation showed medium effects.
- The efficacy for relapse prevention remained robust across different subpopulations for family interventions, family psychoeducation and CBT.
- Overall symptoms were reduced by many of the interventions investigated.
- Family intervention, mindfulness and CBT were associated with improvements in functioning. Integrated intervention was associated with improvement in quality of life.
- Regarding adherence: mindfulness, CBT, integrated intervention and psychoeducation were all superior to TAU and showed large effects.

Remarks

- Although, as described under justifications, many psychosocial interventions had beneficial effects in maintenance therapy, the efficacy of family interventions, family psychoeducation and CBT were most robust (210). Moreover, a subsequent analysis examining only family interventions found that simple family psychoeducation is the most recommendable one.

- *Acceptance and commitment therapy (ACT)*: A manualized third-generation behavioural therapy that incorporates acceptance and mindfulness-based strategies to help individuals in overcoming negative thoughts and feelings.
- *Assertive community treatment*: An intensive, highly integrated approach for community mental health service delivery. The teams visit the individuals at home and provide clinical assessments and crisis interventions, along with psychosocial and functional assistance. This can be considered as a more active form of case management, because it is more holistic and integrated with coordinated services that promote increased wellness for the person.
- *Case management*: Usually each person is assigned to a case manager who contacts them regularly (e.g. once a week) and can provide more intensive support in case of particularly acute needs.
- *Cognitive behavioural therapy (CBT)*: CBT for psychosis is usually based on an individualized case formulation and the establishment of collaborative goals with the person requiring the therapy. Therapy components include the improvement of existing coping strategies, the development and practice of new ones, the modification of delusional beliefs and beliefs about hallucinations and the challenge of dysfunctional schemas. Adaptive views of self are strengthened, including the re-evaluation of negative beliefs about the self.
- *Family interventions*: An intervention involving the individual's relatives, which can have several different aims. These include construction of an

alliance with relatives who care for the person with a psychotic disorder, reduction of adverse family atmosphere, enhancement of the capacity of relatives to anticipate and solve problems, maintenance of reasonable expectations for the person's performance, and attainment of desirable change in relatives' behaviour and belief systems.

- *Family psychoeducation*: Similar to psychoeducation for individuals, the following areas are usually covered for families: symptoms of psychosis, pharmacological and psychosocial treatments, and prevention of relapse, with a special focus on the role of the family. The intervention might be delivered to the relatives alone, involve the individual, or be delivered in a multifamily context. More active aspects such as coping skills might be involved, but the primary focus is the provision of information.
- *Integrated interventions*: Interventions that were explicitly defined as a combination of different treatments, for example individual CBT plus family intervention plus assertive outreach.
- *Mindfulness-based interventions (MF)*: The intervention consists of guided meditation followed by reflective group discussion aimed at facilitating understanding, or metacognitive insight. During meditation, participants bring full awareness to difficult voices, feelings, thoughts and images, and also become aware of habitual coping reactions, safety behaviours and their effects. In meditation they practice letting go of these reactions and learn to observe and allow psychotic experiences to come and go without reacting. Meditation and discussion lead to insight that struggling, judging and ruminating on psychotic experience creates distress, while mindful observation and acceptance of psychotic experience is empowering and calming.
- *Psychoeducation*: Psychoeducation can be defined as the education of a person with a psychiatric disorder in subject areas that serve the goals of treatment and rehabilitation. In individuals with a psychotic disorder, it usually covers the following topics: symptoms of psychosis, models of psychosis, effects and side-effects of medicine, maintenance medicine, psychotherapy for psychosis, early symptoms of relapse and relapse prevention.
- *Rehabilitation*: Usually includes a prevocational day programme, recreational and social activities, apartment living and transitional employment

opportunities with the aim of increasing the ability of the person to function independently in the community.

- *Relapse prevention programmes*: Interventions that generally include education for recognizing early symptoms of relapse, a system of symptoms monitoring, and a crisis plan and intervention in case the symptoms increase over a certain threshold.
- *Telemedicine*: Individuals and their family members are regularly contacted via SMS or telephone call with the main aim of monitoring symptoms. If the symptoms appear to be above a certain threshold, an alert is activated and a visit with the clinician is organized.

Research gaps

- Most of the research is from HICs and, in general, psychological interventions have been developed in HICs. Further research is needed in LMICs.
- Many interventions have so far been investigated in only a few trials and individuals, and thus deserve further study.

Implementation considerations

- Not all forms of psychological interventions may be available in LMICs.
- Attempts should be made to involve family and carers in maintenance treatment.
- Family psychoeducation, a relatively simple intervention that has been proven effective, should be offered in all settings.
- Differences in mental health infrastructure and resources should be considered.
- Variations in cultural context should be considered. There may be acceptability issues.
- Country adaptation and translation of training materials and tools for the provision of psychological interventions is essential.
- Face-to-face psychological interventions delivered by service providers is human resource-intensive as they require substantial provider time, training and supervision.
- Integrating the provision of psychological interventions into primary care provides many advantages, including more holistic health care, increased accessibility of mental health services for people in need of care, opportunities for reducing the stigma of mental health problems and reduced costs.

- For the safe implementation of psychological interventions for people with psychosis by non-specialized professionals, supervision by a mental health specialist is an important aspect that should be considered and planned prior to commencement (209).

PSY12. In adults with bipolar disorder in remission, are psychological interventions (such as psychoeducation, family interventions and CBT) effective?

Recommendation (update):	Individual psychological interventions – namely cognitive behavioural therapy (CBT), family psychoeducation, medicine adherence therapy, online psychoeducation or psychoeducation – should be considered as adjunctive to pharmacological interventions in the treatment of adults with bipolar disorder in remission.	
	Strength of recommendation:	Conditional
	Certainty of evidence:	Low

Justification

- Data were extracted from a systematic review: Oud et al., 2016 (55 trials on the use of psychological interventions for adults with bipolar disorder) (211).
- Individual psychological interventions (CBT, online psychoeducation, psychoeducation, medicine adherence therapy) had a small effect in reducing depressive symptoms. There was no significant effect for mania symptoms or quality of life. There was a medium effect for prevention of relapse.
- Group psychological interventions (psychoeducation, CBT, mindfulness therapy, social cognition, dialectical behaviour therapy [DBT]) had no significant effect for the outcomes in question. There was a large yet non-significant effect for prevention of relapse.
- Family psychoeducation showed a large effect for reduction of depressive and mania symptoms, based only on one small trial, however.
- Integrated cognitive and interpersonal therapy showed a medium-to-large effect for reduction of depressive symptoms, based only on one small study, however. There was a small effect for improved quality of life and no significant effect for mania symptoms.

- The investigated psychological interventions are all listed and defined in [Box 3.2](#).

Remarks

- The majority of people living with bipolar disorder would benefit from maintenance treatment used in the absence of acute symptoms to preserve stability of clinical symptoms and avoid acuity of symptoms, recurrence or relapse.
- In the majority of studies included in the evidence, psychosocial interventions were used adjunctively to medicine, but given the recommendation for psychotropic medicine use for six months, it is still good for psychotherapy to be provided to those not on medicines as well.
- Moderate evidence indicates that psychotherapy is effective in the prevention of relapse and low-quality evidence indicates that it lowers the severity of depressive symptoms (but not mania symptoms).
- There is relative difficulty in providing psychological interventions in LMICs whereas medicine is preferred due to ease and low costs. This is something that needs to be overcome and is also reflected in the lack of research.

BOX 3.2 Investigated psychological interventions and definitions

The investigated interventions included: family psychoeducation, integrated cognitive and interpersonal therapy, individual psychological interventions and group psychological interventions, as listed and defined below.

Family psychoeducation (carers): Intervention for the family only. Psychoeducation about bipolar disorder and its treatment, dealing with one's own functioning (stress and other health risks) and practical advice.

Integrated cognitive and interpersonal therapy: Individuals could choose the group or individual intervention. Psychoeducation, identification of early warning signs, behavioural strategies for coping with symptoms, cognitive strategies, affect-regulation techniques, social network analysis and identification of interpersonal patterns and strategies.

Individual psychological interventions:

- ▶ *Cognitive behavioural therapy (CBT):* Psychoeducation, identifying and modifying dysfunctional and negative thoughts, underlying maladaptive assumptions and beliefs, problem-solving training and strategies for early detection of mood episodes.
- ▶ *Online psychoeducation:* Online interactive programme addressing topics such as the causes of bipolar disorder, diagnosis, treatments, role of lifestyle (changes) and the importance of support.
- ▶ *Individual psychoeducation:* Education on bipolar disorder, causative factors, clinical symptoms and early warning signs, medicine side-effects and coping strategies for mood changes.
- ▶ *Medicine adherence therapy:* Modified cognitive-behavioural intervention aimed at altering cognitions and behaviours that interfere with compliance.

Group psychological interventions:

- ▶ *Group psychoeducation:* Interactive group sessions covering illness and treatment education, symptom monitoring and early detection, treatment adherence, illness management skills, coping strategies and problem solving.
- ▶ *Group CBT:* Psychoeducation, identifying and modifying dysfunctional and negative thoughts, underlying maladaptive assumptions and beliefs, problem-solving training and strategies for early detection of mood episodes.
- ▶ *Group mindfulness therapy:* Psychoeducation, mindfulness meditation (observations of thoughts, feelings and bodily reactions) practice and cognitive therapy regarding depression.
- ▶ *Group social cognition and interaction training:* Emotional training (definition of emotions, facial expression training, understanding of paranoid symptoms as an emotion), role-play social situations (distinguishing facts from guesses, jumping to conclusions, understanding bad events), and integration of learning.
- ▶ *Group dialectical behaviour therapy (DBT):* Psychoeducation about bipolar disorder and treatment. Training of skills: states of mind, reducing vulnerability to emotions, nonjudgemental stance, acceptance, distracting, self-soothing, pros and cons, urge management, self-validation opposite to emotion action, and balancing enjoyable activities with responsibilities.

Source: Oud et al., 2016 (211).

Research gaps

- Most of the evidence is from HICs. Further research is needed in LMICs.
- Reviews investigating the single psychological interventions (separately and not pooling groups and individual interventions) are needed.

Implementation considerations

- Persons with bipolar disorders, similar to all service-users, should be treated with respect and dignity, and provided care based on their consent, in line with human rights instruments, without coercion.
- Attempts should be made to involve families and carers in the treatment. Family psychoeducation, a relatively simple intervention that has been proven effective, should be offered in all settings.
- Not all forms of psychological interventions may be available in LMICs. Differences in availability and accessibility to mental health system infrastructure

and resources should be considered.

- Variations in cultural context should be considered that may have implications on treatment acceptability.
- Country adaptation and translation of training materials and tools for the provision of psychological interventions is essential.
- Face-to-face psychological interventions delivered by service providers are human resource-intensive as they require substantial provider time, training and supervision.
- Integrating the provision of psychological interventions into primary care provides many advantages, including more holistic health care, increased accessibility of mental health services for people in need of care, opportunities for reducing the stigma of mental health problems and reduced costs.

3.11 Self-harm and suicide (SUI)



SUI1. Is safety planning better than treatment as usual for persons with thoughts or plans of self-harm in the last month or acts of self-harm in the last year?

Recommendation (new):	Safety planning type-interventions, i.e. interventions based on principles of safety planning which are multicomponent or supplemented with follow-up or support, can be considered.
Strength of recommendation:	Conditional
Certainty of evidence:	Very low

Justification

- The evidence regarding the effectiveness of safety planning as a stand-alone intervention is insufficient to make a recommendation for its use for persons with thoughts, plans or acts of self-harm. Stallman and Allen (2021) found no eligible studies; there was varied methodological weaknesses across studies, including participants who did not report suicidality, no clear outcome measurement and multiple interventions analysed (212).
- Therefore, this recommendation is focused on safety planning-type interventions. Meta-analysis by Nuij et al. (2021): for safety planning-type interventions (based on safety planning), combined outcome of suicide attempts and mortality was reduced, and suicidal ideation was not (213). A commentary by House (2022) about the meta-analysis concluded that there were important issues with the non-standardized assessment/definition of suicidal behaviour across included studies and that conclusions based on the meta-analysis may have been too generous (214).
- Ferguson et al. (2022) did not proceed with meta-analysis because of the variation in studies (e.g. veterans, refugees) (215). The narrative synthesis concluded an association of safety planning intervention with reduction in suicidal ideation and

behaviour, but less was known regarding reduction of suicide deaths.

Remarks

- The evidence for safety planning as originally defined by Stanley and Brown, 2012 (216) is insufficient, but there is some evidence for safety planning-type interventions based on safety planning to reduce suicide attempts and suicide. Because of practice in the field and due to the value of keeping contact with persons with thoughts, plans or acts of self-harm, interventions based on principles of safety planning can be recommended.

Research gaps

- Well designed, high-quality randomized controlled trials of safety planning, as originally defined, are needed, conducted for the general population with sufficient sample size to assess the outcome of suicide and suicide attempt.
- There is a need to assess the effectiveness and cost effectiveness of safety planning as originally defined. This was beyond the scope of the systematic reviews conducted for this update.
- Furthermore, safety planning as part of a multifaceted intervention would need to be evaluated.

SUI2. Are suicide prevention media campaigns effective in reducing deaths from suicide, suicide attempts and acts of self-harm?

Recommendation:

The evidence regarding effectiveness of stand-alone media campaigns (to raise awareness and sensitize the general public about suicide and its prevention) in reducing deaths from suicide, suicide attempts and acts of self-harm is **insufficient to make a recommendation.**

Remarks

- Identified reviews did not fully satisfy the research question. Studies did not specify a comparator or failed to compare to no intervention, did not involve media campaigns as a stand-alone intervention, and/or had narrow samples (e.g. police only).
- One study met the inclusion criteria, but used ecological-level quasi-experimental design (Till et al., 2013) (217).
- Findings are inconclusive as to the effectiveness of stand-alone mass media campaigns in reducing suicide mortality, acts of self-harm or suicidal thoughts/plans.
- Media campaigns as part of multicomponent interventions (in combination with other interventions) may reduce suicide attempts.

Research gaps

- There is a need for high-quality evaluations of media campaigns for the general population as well as targeted campaigns (e.g. on availability of help), with large enough sample sizes to assess the outcome measures of suicide and suicide attempts.
- Preference should be given to cluster randomized trials and quasi-experimental designs.
- Cultural adaptation when developing media campaigns is always needed.
- Benefits as well as potential harms (particularly when there is a lack of services) of media campaigns need to be addressed and assessed.
- There is need to develop and test public service announcements before they are used in a media campaign.

SUI3. Are stand-alone digital interventions for the self-management of thoughts, plans or acts of self-harm among persons with thoughts or plans of self-harm in the last month or acts of self-harm in the last year effective in reducing deaths from suicide, suicide attempts, acts and thoughts of self-harm?

Recommendation (new):	<p>Stand-alone digital interventions based on evidence-based interventions such as cognitive behavioural therapy (CBT), dialectical behaviour therapy (DBT), problem-solving therapy (PST) and mindfulness should be considered as support for persons with suicidal thoughts.</p>
Strength of recommendation:	Conditional
Certainty of evidence:	Low

Justification

- Evidence was extracted from one systematic review: Sutori et al. (4 RCTs).¹⁵
- The few studies using direct measures to evaluate the critical outcomes of interest of suicides and suicide attempts are underpowered and show no effects.
- There are small, pooled effects favouring the intervention in studies using the important outcome of suicidal thoughts.

Remarks

- Stand-alone digital interventions hold promise for increased scalability and sustainability for the self-management of suicidal thoughts (and of self-harm once evidence of effectiveness was available), which could be especially valuable for LMICs.
- The applicability and health outcomes may be affected by individuals' preferences for human or digital contact.
- Non-specialized health workers can encourage people to use evidence-based digital interventions.
- In situations where no treatment is available at all, the benefits of technology-based suicide preventive interventions may outweigh the risks. One risk may be the loss of resources that could instead be used to implement other, more effective interventions.
- There are concerns regarding potentially sensitive content and data privacy while using digital

health interventions. Measures should be taken to ensure that digital interventions are provided under conditions of safety/security, confidentiality, informed consent and privacy of data. This can include the establishment of standard operating procedures that describe protocols for ensuring consent, data protection and storage, and verifying provider licensing and credentials. Further guidance can be found in the 2019 *WHO guideline: recommendations on digital interventions for health system strengthening* (31).

Research gaps

- All studies were conducted in HICs (Australia, Europe, United States of America). Further research is needed in LMICs.
- Only one RCT was identified that included data on the critical outcome of death by suicide, but it was underpowered to detect an effect. Further studies on the outcome of death by suicide are required.

Implementation considerations

- Costs pertain largely to the technical development phase of setting up and sustaining digital interventions online. Once available on a digital platform, cost of delivery is likely to be low (or lower than interventions delivered by health workers) and there is a high potential to reach a large portion of the population.

¹⁵ Sutori S, Hadlaczky G, Eliasson E, Wasserman D, Carli V. Systematic review and meta-analysis: effectiveness of stand-alone digital suicide preventive interventions for the self-management of suicidality. *J Technol Behav Sci* (under review).

- There may be different preferences by users for human versus digital contact, and geographical variability in access to digital platforms. In delivering digital interventions, there is a need to consider the potential digital divide across population groups with some having unequal access to and skills to use digital technologies. Access might be particularly difficult for certain population groups with poor access to network services, mobile devices or electricity, and/or with low literacy and digital literacy skills. Measures should be taken to address inequities in access to mobile devices so that further inequity is not perpetuated in accessing health information and services, including mechanisms to ensure individuals who do not have access to mobile devices can still receive appropriate services.
- Country adaptation and translation of digital interventions tools with subsequent evaluation is essential.

4. Publication

4.1 Publication and dissemination of the guideline

While the guideline is developed in English, the executive summary will be translated in all of WHO's six official languages.

The guideline and the evidence profiles are available online on the WHO Department of Mental Health and Substance Use's existing [mhGAP Evidence Resource Centre website](#).¹⁶ At the website, there will be active links for each updated or new recommendation providing access to the whole GRADE evidence profile, including references for the evidence that was considered, GRADE tables, narrative descriptions of the evidence that was not inserted into GRADE tables and considerations on preferences, values and feasibility issues.

Relevant departments in ministries of health will be notified of the updated guideline through WHO regional and country offices. A briefing package will be prepared for technical officers outside of WHO headquarters, including an executive summary and a Q&A document related to policy and programme implications. In particular, the briefing materials will highlight the changes (updates) and the new recommendations presented in this guideline.

The media will be notified of the updated mhGAP guideline. Capacity-building activities will be undertaken through regional and subregional meetings and other activities related to mhGAP and implementation of four WHO action plans: the *Comprehensive mental health action plan 2021–2030* (14), the *Intersectoral global action plan on epilepsy and other neurological disorders 2022–2031* (3), the *Global action plan on the public health response to dementia 2017–2025* (15), and the *Global alcohol action plan 2022–2030* (16).

4.2 Derivative products

As part of the scaling-up strategy of mhGAP in countries, derivative products based on the mhGAP guideline have been developed and will be revised to reflect the changes in this mhGAP guideline. This mhGAP guideline will be incorporated into an updated edition of the mhGAP intervention guide (mhGAP-IG). The mhGAP-IG translates the evidence-based recommendations into simple clinical protocols and algorithms to facilitate decision-making for assessment and management. It is aimed at non-specialist health workers working at primary- and secondary-level health-care facilities. The mhGAP-IG is also intended for use by health-care planners and programme managers working in close conceptual and strategic synergy with the WHO *Comprehensive mental health action plan 2013–2030* (14). It includes additional details that are beyond the scope of the guideline, such as optimal duration of therapy, maximum daily dose, when to stop the therapy, when to refer, default criteria, toxicity and drug–drug interactions. This mhGAP guideline will be similarly incorporated into other mhGAP implementation materials, including *mhGAP humanitarian intervention guide (mhGAP-HIG)* (218), *mhGAP-IG App (e-mhGAP)*, *mhGAP training manuals* (219), *mhGAP operations manual* (209), *mhGAP community toolkit* (220) and the mhGAP e-learning course, which is being developed with the WHO Academy.

4.3 WHO model list of essential medicines (EML)

The EML and EMLc includes products for MNS disorders in the areas of psychotic disorders, mood disorders, anxiety, substance use and epilepsy (13,132). The updated recommendations for any psychotropic medicines will be used to inform the EML and EMLc and to promote affordable access to quality, safe and effective medicines for MNS disorders.

¹⁶ <https://www.who.int/teams/mental-health-and-substance-use/treatment-care/mental-health-gap-action-programme/evidence-centre>

5. Monitoring and evaluating the impact of the guideline

After the publication of this mhGAP guideline, WHO will continue to collect regular feedback from implementation activities to evaluate their usefulness and impact. WHO will additionally continue to collect feedback from international experts and health workers who are familiar with using the mhGAP guideline. This information will be used to evaluate the effects of the guideline on processes and health outcomes and to ensure the quality of the guideline and identify areas to be improved. This will draw on existing WHO resources

where possible, including the *Atlas: country resources for neurological disorders* (23), the *Comprehensive mental health action plan 2013–2030* (14), the *Mental health atlas 2020* (24), indicators provided as part of implementing WHO's *Intersectoral global action plan on epilepsy and other neurological disorders 2022–2031* (3), the *Global action plan on the public health response to dementia 2017–2025* (15) and the *Global alcohol action plan 2022–2030* (16).

6. Updating the evidence

The guideline will be updated five years after publication. The WHO Steering Group will continue to follow the research developments in the mhGAP module areas, particularly those questions for which no evidence was found and those that were supported by low-certainty evidence, where new recommendations

or a change in the published recommendation may be warranted, respectively. Following publication and dissemination of the guideline, any concern about validity of any recommendation would be promptly communicated to the guideline implementers in addition to plans to update the recommendation.



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Annex 1.

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Annex 2.

Managing declarations of interest and conflicts of interest

All contributors declared no interests, with the exception of those listed below. A summary of declared interests and how they were managed is provided below.

Declared interests of the members of the Guideline Development Group (GDG)

Name and title	Declaration of interest	Conflict of interest and management
Dr Amza Ali	Employed and holds stocks, shares and a commercial interest in Psyence Group.	The Psyence group is a biotechnology company developing psychedelic therapies. The nature of the company was not considered to represent a conflict as psychedelic therapy is not included anywhere in mhGAP and was not a part of any of the PICO question discussions. No conflict of interest identified.
Professor Sawitri Assanangkornchai	None	No conflict of interest identified.
Professor Henry Brodaty	Employed by the University of New South Wales, Sydney. Payment for consultancy or advisory board membership for Biogen Pharmaceuticals, Cranbrook Care, Nutricia Australia, Roche, Skin2Neuron. Ongoing research support from Australia's National Health Medical Research Council (NHMRC) and the Commonwealth Department of Health (Australian Government). Honorary Advisor to Alzheimer's Disease International, Dementia Australia and Montefiore Homes, Sydney.	No conflict of interest identified.

Name and title	Declaration of interest	Conflict of interest and management
Dr Vladimir Carli	Shareholder of Mental Health in Mind International AB. Senior lecturer at the Swedish National Centre for Suicide Research and Prevention, Karolinska Institute.	No conflict of interest identified.
Dr Odille Chang	None	No conflict of interest identified.
Professor Pamela Y. Collins	None	No conflict of interest identified.
Professor Pim Cuijpers	None	No conflict of interest identified.
Professor Petrus J. de Vries	On the executive committee of four international non-profit associations/societies that have a direct interest and focus on child and adolescent mental health and/or neurodevelopmental disabilities.	No conflict of interest identified.
Professor Christopher Dowrick	Chair (unpaid) of World Organisation of Family Doctors (WONCA) Working Party for Mental Health 2016–2021. Research funding from English National Institute for Health Research and European Commission until 2020. Recent funding from Novartis and WONCA for primary care mental health educational activities.	No conflict of interest identified.
Dr Julian Eaton	Employed by CBM Global and London School of Hygiene and Tropical Medicine (LSHTM) Centre for Global Mental Health. Unpaid involvement with the Inter-Agency Standing Committee (IASC), Mental Health Innovation Network (MHIN), research advisory groups (SPARK, HOPE, INDIGO) and journal boards (Global Mental Health, Intervention). These are all civil society, intergovernmental and research organizations involved in global mental health.	No conflict of interest identified.
Dr Rabih El Chammay	None	No conflict of interest identified.
Professor Cleusa P. Ferri	None	No conflict of interest identified.
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Name and title	Declaration of interest	Conflict of interest and management
Dr Michael P. Hengartner	None	No conflict of interest identified.
Dr Asma Humayun	None	No conflict of interest identified.
Professor Nathalie Jette	Chair of International League Against Epilepsy (ILAE) Standards and Best Practice Council, Bludhorn Professor of International Medicine (Research Chair), honorarium for role as associate editor of <i>Epilepsia</i> .	No conflict of interest identified.
Dr Maria Elena Medina-Mora	None	No conflict of interest identified.
Professor Pratima Murthy	None	No conflict of interest identified.
Dr Dinah Nadera	Consulting, including service as a technical advisor and mhGAP trainer for CBM International. Pt 15 000 in 2019. Support (including honoraria) for being on a speaker's bureau, giving speeches or training for a commercial entity or other organization with an interest related to the subject of the meeting or work. Department of Health (Philippines) Region 13, Bangsamoro Autonomous Region of Muslim Mindanao (BARMM). Pt 12 000–15 000. 2018 (Region13), 2019 (Region 13 and BARMM), 2020 (BARMM).	No conflict of interest identified.
Professor Charles Newton	None	No conflict of interest identified.
Mr Michael Njenga	Extensively worked in the area of human rights for persons with psychosocial disabilities in various capacities. Lead trainer for the Convention on the Rights of Persons with Disabilities (CRPD)/ Sustainable Development Goals (SDGs) Bridge cycles for the International Disability Alliance since the year 2016. Has given numerous talks in the area of human rights at WHO, CRPD Committee and various universities.	No conflict of interest identified.
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Name and title	Declaration of interest	Conflict of interest and management
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Professor Afarin Rahimi-Movaghar	None	No conflict of interest identified.
Professor Atif Rahman	Employment at University of Liverpool, United Kingdom. Provided technical advice to the Human Development Research Foundation and Shifa Tameer-e-Millat University. Research funding from the National Institute of Health Research, United Kingdom; National Institute of Mental Health, USA; MRC, United Kingdom	No conflict of interest identified.
Professor Shekhar Saxena	None	No conflict of interest identified.
Ms Charlene Sunkel (member withdrew from GDG)	None	No conflict of interest identified.
Professor Sir Graham Thornicroft	Board member, United for Global Mental Health. Board member, Mental Health and Human Rights (F-GIP). Board Chair, Implemental (formerly Maudsley International). Supported by the NIHR Applied Research Collaboration South London at King's College London NHS Foundation Trust, and by the NIHR Asset Global Health Unit award. The views expressed are those of the author(s) and not necessarily those of the United Kingdom's National Health Service (NHS), the NIHR or the Department of Health and Social Care. Supported by the Guy's and St Thomas' Charity for the On Trac project (EFT151101), and by the MRC in relation to the Emilia (MR/S001255/1) and Indigo Partnership (MR/R023697/1) awards.	No conflict of interest identified.

Name and title	Declaration of interest	Conflict of interest and management
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DFID: Department for International Development; IASC: Inter-Agency Standing Committee; MRC: Medical Research Council (of UKRI); NHMRC: National Health Medical Research Council (Australia); NHS: National Health Service (United Kingdom); NIH: National Institutes of Health (USA); NIHR: National Institute for Health and Care Research (United Kingdom); UKRI: UK Research and Innovation (United Kingdom).

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Professor Helen Herrman	President and officer, World Psychiatric Association, 2014–2020.	No conflict of interest identified.
Dr Lola Kola	None	No conflict of interest identified.
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Professor David Ndeti	None	No conflict of interest identified.
Dr Alfredo Pemjean	None	No conflict of interest identified.
Professor Pratap Sharan	None	No conflict of interest identified.

Name and title	Declaration of interest	Conflict of interest and management
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Dr Gagandeep Singh	Department of Biotechnology, Wellcome Trust India Alliance (Rs 9 99 00 000). Chairperson, International League Against Epilepsy, Primary Care Task Force. Epilepsy Telemetry Brief, WHO (Rs 500 000).	No conflict of interest identified.
Dr David Shiers	Fee for attendance at National Clinical Audit of Psychosis at Royal College of Psychiatrists (£416 on two occasions in 2019–2020). Expert advisor to the National Institute for Health and Care Excellence (NICE), England. Honorary reader in early psychosis, University of Manchester. Honorary research consultant, Psychosis Research Trust, Greater Manchester Mental Health NHS Trust, Honorary Senior Research Fellow, Primary Care and Health Sciences, Keele University, Staffordshire. Lay member of NICE guideline development group NG181 (Rehabilitation for adults with complex psychosis) in 2019–2020 (£150 free per day for nine days in 2019/2020). Lecture on MSc course at University of London annually from 2016 (annual fee of £100–130 plus reimbursement of expenses). Royalty of £20 annually from Wiley Blackwell Publications for the 2010 publication <i>Promoting recovery in early psychosis</i> . Honorary co-applicant on research grants.	No conflict of interest identified.
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