Update of the Mental Health Gap Action Programme (mhGAP) Guideline for Mental, Neurological and Substance use Disorders

WHO mhGAP Guideline Update

May 2015

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Executive summary

Background and objectives

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 2008, the World Health Organization (WHO) developed the Mental Health Gap Action Programme (mhGAP), to facilitate scaling up of care for MNS disorders. A key part of mhGAP is the evidence-based guideline, published in 2010 and available through the mhGAP Evidence Resource Centre (http://www.who.int/mental_health/mhgap/evidence/en/). The objectives of the guideline are:

- To provide up-to-date WHO guidance to facilitate delivery of interventions by non-specialist health care providers in low- and middle-income countries (LAMICs);
- To assist with the scale up of care for MNS disorders identified as conditions of high priority in LAMICs, specifically: depression, psychosis (including schizophrenia and bipolar disorders), epilepsy, child mental disorders, dementia, alcohol use disorders, drug use disorders and self-harm/suicide;
- To provide up-to-date WHO guidance that will facilitate the implementation of the WHO *Comprehensive Mental Health Action Plan 2013-2020* by health care planners and programme managers in LAMICs.

As evidence-based guidelines are designed to reflect current research, regular update is of paramount relevance.[1] Out-of-date recommendations could be one determinant of inadequate patient care: therefore, conducting regular evaluations and performing updates when appropriate should ensure the validity of recommendations. More than four years have passed since the mhGAP recommendations have been issued. Since then, regular monitoring of the background evidence has been performed by the WHO Collaborating Centre assisting with the mhGAP guideline process in order to highlight areas where update is appropriate. Furthermore, feedback from technical experts and health care providers has been collected, together with feedback from several implementation activities. All of these activities prompted WHO to consider that, in order to maintain the validity of the mhGAP guideline, an update is warranted.

Target audience

The primary audience for the mhGAP guideline are non-specialized health-care providers working at first- and second-level health-care facilities. These include physicians who are not mental health specialists, family physicians, nurses and clinical officers or other cadres of health workers. The secondary audience includes health care managers including national, regional and district level programme managers responsible for primary or non-mental health secondary health care services and specialists (in mental health, neurology and substance use) involved in training of trainers and supervision.

Guideline update methodology

The Guideline Development Group (GDG) members, the technical experts (to assist with evidence review and synthesis), and the peer reviewers were selected from an international panel of experts with

[1] Lyratzopoulos G, Barnes S, Stegenga H, Peden S, Campbell B., International Journal of Technology Assessment in Health Care. 2012;28(1): 29–35. doi: 10.1017/S0266462311000675.

multidisciplinary expertise. The evidence review and synthesis process as well as the recommendations were developed in accordance with the procedures outlined in the WHO Handbook for Guideline Development.

Methods for evidence synthesis

The key questions from the current mhGAP guideline were reviewed and areas where update was appropriate were identified based on the feedback from implementation activities, health care providers and regular monitoring of evidence. New key questions were identified based on the feedback received from users of the mhGAP guideline in the countries. There were 29 key questions used to update the guideline. These were formulated using the PICO framework (Population, Intervention, Comparator, Outcome). The review and synthesis of evidence was carried out through systematic searches. For each of the key questions included in the update process, an evidence profile was constructed using WHO guideline development procedures. Evidence profiles summarise the evidence retrieved, provide the assessment of the quality of evidence wherever possible using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology, and present discussion of values, preferences, benefits, harms and feasibility.

Translating evidence into recommendations

Within the evidence profile, the section entitled "evidence to recommendations" presents a synopsis of the evidence (benefits and harms of the intervention) and the quality of evidence according to the GRADE approach, and it discusses values and preferences and the feasibility of the intervention under consideration. Based on the evaluation of the above criteria, the GDG proposed the strength of each recommendation as either strong or conditional.

A "strong" recommendation suggests that the GDG agreed that the quality of the evidence combined with certainty about the values and preferences and the feasibility of the recommendation meant it should be followed in all or almost all circumstances. A "conditional" recommendation suggests less certainty about the quality of evidence and variation values and preferences and feasibility, leading to circumstances in which the recommendation may not apply.

Summary of recommendations

The following table summarizes the recommendations for the mhGAP Guideline Update 2015. They should be read together with their corresponding remarks reported later in this document. Definition and description of interventions, together with the evidence retrieved and analysis of values and preferences and feasibility issues leading to these recommendations can be found in individual evidence profiles.

mhGAP Priority Condition	Recommendation
Depression	**DEP1. Antidepressant medication in comparison with psychological treatment for moderate-severe depressive disorder *[New 2015]***
	As first-line therapy, health care providers may select psychological treatments (such as behavioural activation [BA], cognitive behavioural therapy [CBT], or interpersonal psychotherapy [IPT]) or antidepressant medication (such as selective serotonin reuptake inhibitors [SSRIs] and tricyclic antidepressants [TCAs]). They should keep in mind the possible adverse effects associated with antidepressant medications, the ability to deliver either intervention (in terms of expertise, and/or treatment availability), and individual preferences.

(Conditional recommendation. Low quality of evidence)

DEP2. Comparative effectiveness of different formats of psychological treatments for depressive disorder ***[New 2015]***

Health care providers can offer different treatment formats of WHO's recommended, structured psychological interventions for adults and older adolescents with depressive disorder. These include behavioural activation, cognitive behavioural therapy (CBT), interpersonal psychotherapy (IPT), problem-solving treatment as an adjunct treatment (e.g. in combination with antidepressants). Different treatment formats for consideration include (a) individual and/or group face-to-face psychological treatments delivered by professionals and supervised lay therapists, as well as (b) self-help psychological treatment.

While face-to-face psychological treatment or guided self-help psychological treatment are likely to have better outcomes than unguided self-help, the latter may be suitable for those people who either (a) do not have access to face-to-face psychological treatment or guided self-help psychological treatment or (b) are not willing to access such treatments.

(Conditional recommendation. Low quality of evidence.)

Psychosis including schizophr-enia and bipolar disorder	**PSY1. Role of depot antipsychotic medication in long-term antipsychotic treatment *[Updated 2015]*** In people with psychotic disorders (including schizophrenia) requiring long-term antipsychotic treatment, depot antipsychotics can be offered instead of oral medications as part of a treatment plan. *(Conditional recommendation. Very Low quality of evidence.)* **PSY2. Antipsychotics and mood stabilizers (lithium, valproate, or carbamazepine) for maintenance treatment of bipolar disorder *[Updated 2015]*** Lithium or valproate or certain second-generation antipsychotics (*aripiprazole, olanzapine, paliperidone extended release, quetiapine, and risperidone long acting injection release*) can be offered for the maintenance treatment of bipolar disorder. If treatment with one of these agents is not feasible, first-generation antipsychotics or carbamazepine may be used. Maintenance treatment should be offered in primary health care settings under supervision of a specialist. *(Conditional recommendation. Low quality of evidence.)* **PSY3. Recovery-oriented psychosocial strategies enhancing independent living and social skills (such as life skills and social skills training) *[2015]*** Recovery-oriented psychosocial interventions (e.g. life skills and social skills training) to enhance independent living skills can be offered for people with psychotic disorders (including schizophrenia and bipolar disorder) and for their families and/or caregivers. Facilitation of assisted living, independent living and supported housing that is culturally and contextually appropriate may be considered as an option for people with psychotic disorders (including schizophrenia and bipolar disorder). Careful consideration should be given to the functional capacity and the need for stability and support when advising and facilitating optimal housing arrangements. *(Conditional recommendation. Very Low quality of evidence)* **PSY4. Recovery-oriented strategies enhancing vocational and economic inclusion (such as supported employment) *[2015]*** Recovery-oriented strategies enhancing vocational and economic inclusion (e.g. supported employment) can be offered for people with psychosis (including schizophrenia and bipolar disorder). Such strategies should be contextualised to their social and cultural environment, using formal and non-formal recovery-oriented interventions that may be available, and using a multisectoral approach. *(Conditional recommendation. Low quality of evidence)*

	PSY5. Second-generation antipsychotic medications in psychotic disorders (including schizophrenia) ***[New 2015]***
	Second-generation antipsychotics (with the exception of clozapine which is indicated for treatment resistant psychosis) can be offered for the treatment of psychotic disorders (including schizophrenia). There is no clinically relevant advantage of one second-generation antipsychotic over others and choice should be based on availability, cost, patient preferences and possible adverse effects associated with each medication. *(Conditional recommendation. Low quality of evidence)*
	PSY6. Pharmacological interventions in adolescents with psychotic disorders (including schizophrenia and bipolar disorder) ***[New 2015]***
	In adolescents with psychotic disorders (including schizophrenia and bipolar disorder), certain second-generation antipsychotic medications (aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone) can be offered as a treatment option under supervision of a specialist. If treatment with one of the above agents is not feasible, first-generation antipsychotics (haloperidol, chlorpromazine, perphenazine, molindone) may be used under supervision of a specialist. *(Conditional recommendation. Very low quality of evidence)*
Epilepsy	**EPI1. Anti-epileptic medications for management of acute convulsive seizures when no intravenous access is available** ***[Updated 2015]***
	When intravenous access is not available for the control of acute seizures in adults, non- parenteral routes of benzodiazepine administrations should be used. Options include rectal diazepam, buccal or intranasal midazolam, rectal or intranasal lorazepam. The preference may be guided by availability, expertise and social preference. Some benzodiazepines (lorazepam or midazolam) may be given by intramuscular route, which requires additional expertise. Intramuscular administration of diazepam is not recommended because of erratic absorption. *(Strong recommendation. Low quality of evidence)*
	EPI2. First-line anti-epileptic medication for management of acute convulsive seizures, when intravenous access is available ***[2015]***
	In adults presenting with acute convulsive seizures where intravenous access is available, either intravenous lorazepam or diazepam can be administered to terminate the seizure. Intravenous lorazepam (if available) may be preferred over intravenous diazepam because of slightly superior benefit-risk profile.

(Conditional recommendation. Low quality of evidence)

EPI3: Anti-epileptic medications for management of established status epilepticus *[Updated 2015]*

In adults with established status epilepticus, i.e. seizures persisting after two doses of benzodiazepines, either intravenous valproic acid, intravenous phenobarbital or intravenous phenytoin can be used with appropriate monitoring.

Intravenous valproic acid is preferred over intravenous phenobarbital or intravenous phenytoin because of its superior risk-benefit profile. The choice of these medications depends on local resource settings, including availability and facilities for monitoring.

Where intravenous infusion may not be feasible, intramuscular phenobarbital remains an option, with appropriate monitoring. Phenytoin and valproic acid should not be given intramuscularly.

(Conditional recommendation. Very Low quality of evidence)

EPI4: Anti-epileptic medications for adults and children with HIV *[New 2015]*

In comparison with enzyme-inducing anti-epileptic medications (phenobarbital, phenytoin, carbamazepine) or valproic acid, newer generation anti-epileptic medications that are not hepatically metabolized (i.e. leviteracetam, lacosamide, topiramate, gabapentin and pregabalin) may be preferred to use in people with HIV on certain antiretroviral medications (protease inhibitors or non-nucleoside reverse-transcriptase inhibitors).

If the treatment with newer generation anti-epileptic medications is not feasible, valproic acid is preferred over the enzyme-inducing anti-epileptic medications (phenobarbital, phenytoin, and carbamazepine). In all cases, close monitoring of HIV viral load and regular clinical monitoring is required. If resources are available, anti-epileptic medication levels should be monitored.

(Conditional recommendation. Very Low quality of evidence)

EPI5: Anti-epileptic medicines for medication resistant convulsive epilepsy *[New 2015]*

Certain newer anti-epileptic medications (lamotrigine, levetiracetam and topiramate) should be offered as add-on therapy in patients with medication resistant convulsive epilepsy.

The essential anti-epileptic medications (carbamazepine, phenobarbital, phenytoin, and valproic acid) may be of benefit as add-on therapy in patients with medication resistant convulsive epilepsy.

(Conditional recommendation. Moderate quality of evidence)

Mental disorders with childhood onset	**CH1. Caregiver skills training for management of developmental disorders *[Updated 2015]*** Caregiver skills training should be provided for management of children and adolescents with developmental disorders, including intellectual disabilities and pervasive developmental disorders (including autism). *(Strong recommendation. Low quality of evidence)* **CH2. Psychosocial interventions for treatment of behavioural disorders *[Updated 2015].*** Behavioural interventions for children and adolescents, and caregiver skills training, may be offered for the treatment of behavioural disorders. *(Conditional recommendation. Low quality of evidence)* **CH3: Psychosocial interventions for treatment of emotional disorders *[Updated 2015]*** Psychological interventions, such as cognitive behavioural therapy (CBT), interpersonal psychotherapy (IPT) for children and adolescents, and caregiver skills training focused on their caregivers, may be offered for the treatment of emotional disorders. *(Conditional recommendation. Low quality of evidence)* **CH4: Antidepressants among adolescents with moderate-severe depressive disorder for whom psychosocial interventions have proven ineffective *[2015]*** When psychosocial interventions prove ineffective, fluoxetine (but not other Selective Serotonin Reuptake Inhibitors or Tricyclic Antidepressants) may be offered in adolescents with moderate-severe depressive episode/disorder. The intervention should only be offered under supervision of a specialist. *(Conditional recommendation. Very Low quality of evidence)* **CH5: Effective strategies for detecting maltreatment of children and youth within the context of mental health and developmental assessment *[New 2015]*** Health care providers should be alert to the clinical features associated with child maltreatment and associated risk factors and assess for child maltreatment, without putting the child at increased risk. *(Conditional recommendation. Very Low quality of evidence)*

	CH6: Community-based rehabilitation for adults with developmental disorders including intellectual disabilities and autism spectrum disorders *[New 2015]*
	Non-specialized health care providers can offer supporting, collaborating and facilitating referral to and from community based rehabilitation (CBR) programmes, if available, for care of adults with developmental disorders, including intellectual disabilities and pervasive developmental disorders (including autism). *(Conditional recommendation. Very Low quality of evidence)*
Dementia	**DEM1: Cholinesterase inhibitors and memantine for treatment of dementia *[Updated 2015]***
	Cholinesterase inhibitors and memantine may be offered for people with dementia in non-specialist health settings. Non-specialists need to be trained and supervised to ensure competence in diagnosis and monitoring. The use of cholinesterase inhibitors should be focused upon those with mild to moderate Alzheimer's disease, where the majority of evidence is available. Memantine may be considered for those with moderate to severe Alzheimer's disease and vascular dementia. Memantine should not be prescribed for Lewy Body dementia. *(Conditional recommendation. Very Low quality of evidence)*
	DEM2 Psychological therapies for people with dementia who have associated depression *[New 2015]*
	People with dementia and mild to moderate symptoms of depression may be offered psychological interventions (such as cognitive behavioural therapy [CBT], interpersonal therapy [IPT], structured counselling and behavioural activation therapy), in non-specialized health care settings under supervision of a specialist. *(Conditional recommendation. Low quality of evidence)*
	DEM3: Pharmacological interventions (antidepressants) for people with dementia who have associated depression *[2015]*
	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]) may be considered. In people with dementia and mild to moderate depression, antidepressants should not be offered as a first-line treatment. *(Conditional recommendation. Low quality of evidence)*

	DEM4: Oral nutrition supplementation or dietary education for caregivers for managing people with dementia at risk for undernutrition or currently undernourished *[New 2015]* In people with dementia who are at risk of undernutrition, dietary advice aimed at food fortification should be tried first, and weight and nutritional status monitored. If nutritional status is not improved, then oral nutritional supplementation should be used (in the absence of any clinical contraindication) to achieve weight gain and restore nutritional status. *(Strong recommendation. Low quality of evidence)* **DEM5: Nutritional interventions for people with dementia or cognitive impairment *[New 2015]*** In people with either cognitive impairment or dementia, supplementation with nutrients, or use of Gingko biloba extracts should not be considered to improve cognitive function, to reduce the risk of developing dementia, or to slow the progression of dementia once established. When feasible, dietary deficiencies should be investigated and monitored in those with dementia and appropriate supplementations should be provided. *(Conditional recommendation. Very Low quality of evidence)*
Alcohol use disorders	**ALC1: Baclofen for relapse prevention and management among people with alcohol dependence *[New 2015]*** Baclofen can be offered to prevent relapse among people with alcohol dependence post-detoxification. *(Conditional recommendation. Low quality of evidence)* **ALC2: Psychosocial interventions for the management of alcohol dependence *[2015]*** Psychosocial interventions including cognitive behavioural therapy (CBT), couples therapy, psychodynamic therapy, behavioural therapies, social network therapy, contingency management and motivational interventions, and twelve- step facilitation can be offered for the treatment of alcohol dependence. *(Conditional recommendation. Low quality of evidence)*

Drug use disorders	**DRU1: Psychosocial interventions for the management of cannabis dependence *[Updated 2015]*** Psychosocial interventions based on cognitive behavioural therapy or motivational enhancement therapy (MET) or family therapy can be offered for the management of cannabis dependence. *(Conditional recommendation. Low quality of evidence)* **DRU2: Psychosocial interventions for the management of psychostimulant dependence *[2015]*** Psychosocial interventions including contingency management, and cognitive behavioural therapy (CBT) and family therapy can be offered for the treatment of psychostimulant dependence. *(Conditional recommendation. Very Low quality of evidence)* **DRU3: Supervised dosing with a long acting opioid medication for the management of prescription opioid dependence *[New 2015]*** When managing people who are dependent on strong prescription opioids (i.e. morphine-like), physicians can switch to a long acting opioid (such as methadone and buprenorphine) which can be taken once daily, with supervised dispensing if necessary, either for maintenance treatment or for detoxification. *(Conditional recommendation. Low quality of evidence)*
Self-harm and suicide	**SUI1. School-based interventions for reducing deaths from suicide and suicide attempts among young people *[New 2015]*** The implementation of suicide prevention programmes in school settings that include mental health awareness training and skills training can be offered to reduce suicide attempts and suicide deaths among adolescent students. *(Conditional recommendation. Low quality of evidence)*

Introduction

Background and context

Mental, neurological, and substance use (MNS) disorders are prevalent in all regions of the world and are major contributors to morbidity and premature mortality. The Global Burden of Disease study 2010 (GBD) estimated that MNS disorders account for 183.9 million disability-adjusted life years (DALYs), or 7.4% of all DALYs worldwide.[1] In 2010, MNS disorders were the leading cause of years lived with disability (YLDs) worldwide.[2] The stigma and violations of human rights directed towards people with these disorders compound the problem. The resources that have been provided to tackle the huge burden of MNS disorders are insufficient, inequitably distributed and inefficiently used. The result is a large treatment gap which is more than 75% in many low-and middle-income countries (LAMICs).[3]

In order to reduce the gap and to enhance the capacity of Member States to respond to the growing challenge, the World Health Organization (WHO) developed the Mental Health Gap Action Programme (mhGAP).[1] 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 LAMICs.

Existing mhGAP guideline

The 2010 mhGAP evidence-based guideline for MNS disorders was developed following the WHO Handbook for Guideline Development. It was published electronically in the mhGAP Evidence Resource Centre, a web-based resource that contains the background materials, process documents, evidence profiles and recommendations (http://www.who.int/mental_health/mhgap/evidence/en/).

As part of the mhGAP scaling up strategy in Member States, derivative products based on the mhGAP guideline were developed, including the *mhGAP Intervention Guide (mhGAP-IG) for mental, neurological and substance use disorders in non-specialized health settings*,[4] and other accompanying training and implementation materials.

Why a guideline update is needed

In May 2013, the 66th World Health Assembly adopted WHO's Comprehensive Mental Health Action Plan 2013-2020.[5] The Action Plan recognizes the essential role of mental health in achieving health for all people. It indicates, as one of its cross-cutting principles that mental health strategies and interventions for treatment, prevention and promotion need to be based on scientific evidence and/or best practice, taking cultural considerations into account. As a consequence, the Mental Health Action Plan builds upon the work of the mhGAP programme and its implementation is based on mhGAP products, including the evidence-based guideline for MNS disorders, mhGAP-IG and accompanying training and implementation materials.

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[2] Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ., Global burden of disease attributable to mental and substance use disorders: findings of the Global Burden of Disease Study 2010. Lancet 2013; 382:(9904): 1575-1586. doi: 10.1016/S0140-6736(13)61611-6.

3 WHO. mhGAP Mental Health Gap Action Programme. Scaling up care for mental, neurological, and substance use disorders. Geneva: World Health Organization, 2008. (http://www.who.int/mental_health/mhgap_final_english.pdf, accessed Spring 2015).

[4] mhGAP Intervention Guide for mental, neurological and substance use disorders in non-specialized health settings. Geneva: World Health Organization, 2010. (http://whqlibdoc.who.int/publications/2010/9789241548069_eng.pdf, accessed Spring 2015).

[5] WHO. Mental health action plan 2013 – 2020. Geneva: World Health Organization; 2013 (http://apps.who.int/iris/bitstream/10665/89966/1/9789241506021_eng.pdf, accessed Spring 2015).

As evidence-based guidelines are designed to reflect current research, regular update is of paramount relevance.[6] Out-of-date recommendations could be one determinant of inadequate patient care: therefore, conducting regular evaluations and performing updates when appropriate should ensure the validity of recommendations.

More than four years have passed since the mhGAP recommendations have been issued. Since then, regular monitoring of the background evidence has been performed by the WHO Collaborating Centre assisting with the mhGAP guideline process in order to highlight areas where update is appropriate. Furthermore, feedback from technical experts and health care providers has been collected, together with feedback from several implementation activities. All of these activities prompted WHO to consider that, in order to maintain the validity of the mhGAP guideline, an update is warranted.

WHO guidelines and products related to the existing and updated guidelines

The updated mhGAP guideline will be used to maintain the validity of the mhGAP Evidence Resource Centre: a repository of background material, process documents, evidence profiles and recommendations in electronic format, organized around the mhGAP priority conditions (http://www.who.int/mental_health/mhgap/evidence/en/).

The mhGAP guideline also forms the basis of mhGAP derivative materials, including the mhGAP Intervention Guide (mhGAP-IG) and implementation materials. The mhGAP-IG is a technical tool, based on the mhGAP guideline, which gives guidance for the management of MNS disorders, developed for non-specialist health settings (http://www.who.int/mental_health/publications/mhGAP_intervention_guide/en/). Other mhGAP implementation materials developed to assist countries in implementing the mhGAP guideline and interventions include mhGAP training materials, as well as other toolkits and process documents.

There are other relevant guidelines: A *Guideline for the management of conditions specifically related to stress* (http://www.who.int/mental_health/emergencies/stress_guidelines/en/) and a *guideline for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence* (http://www.who.int/substance_abuse/publications/drugs/en/). These guidelines were produced in 2013 and 2014 respectively; therefore, they are not due to be updated and were not included in this guideline update.

Some recommendations from the mhGAP updated guideline on epilepsy and seizures will be linked to Paediatric Emergency Triage Assessment and Treatment Guidelines on Fluids, Oxygen therapy and Seizures, which are currently being finalized.

Objectives of the Guideline update

This guideline is an update of the existing mhGAP guideline for MNS disorders.

The mhGAP guideline has the following objectives:

- To provide up-to-date WHO guidance to facilitate delivery of interventions by non-specialist health care providers at primary and secondary care facilities in LAMICs.

[6] Lyratzopoulos G, Barnes S, Stegenga H, Peden S, Campbell B., International Journal of Technology Assessment in Health Care. 2012;28(1): 29–35. doi: 10.1017/S0266462311000675.

- To assist with the scale up of care for MNS disorders identified as conditions of high priority in LAMICs, specifically: depression, psychosis (including schizophrenia and bipolar disorders), epilepsy, child mental disorders, dementia, alcohol use disorder, drug use disorders and self-harm/suicide.
- To provide up-to-date WHO guidance that will facilitate implementing the WHO *Comprehensive Mental Health Action Plan 2013-2020* by health care planners and programme managers in LAMICs.

Target audience

This guideline update focuses on the same target audience as for the first edition of mhGAP guideline: health care providers working at a first- or second-level facility or at district level, including basic outpatient and inpatient services. The health care providers could be doctors, nurses or other cadres of health workers. It is also aimed to be used by health care planners and programme managers including national, regional and district level programme managers responsible for primary or non-mental health secondary care services and specialists (in mental health, neurology and substance use) involved in training of trainers and supervision.

Scope of guideline: What is included in this update?

The first edition of the mhGAP guideline included guidance on evidence-based interventions to identify and manage a number of priority conditions (depression, psychosis, bipolar disorders, epilepsy and seizures, mental disorders in children and adolescents, dementia, alcohol use disorders, drug use disorders, and self-harm/suicide). These priority conditions were selected because they represent a large burden in terms of mortality, morbidity and disability, have high economic costs, and are associated with human rights violations.

The list of key questions and recommendations issued in 2010 were reviewed for the update process. After the publication of the 2010 mhGAP guideline, more evidence and programmatic experience has become available. This revision took the following factors into careful consideration:

(a) New evidence that has been produced: From 2010 onwards regular updates of the evidence base have been carried out using appropriate search strategies;

(b) Feedback from WHO implementation activities: From 2010 onwards, WHO has implemented several programmes in LAMICs that were based on mhGAP recommendations and has also collected suggestions and proposals for future revisions;

(c) Feedback from experts and health care providers: Feedback was collected from international experts and health care providers who are familiar with using mhGAP recommendations and related products by means of a standardized form.

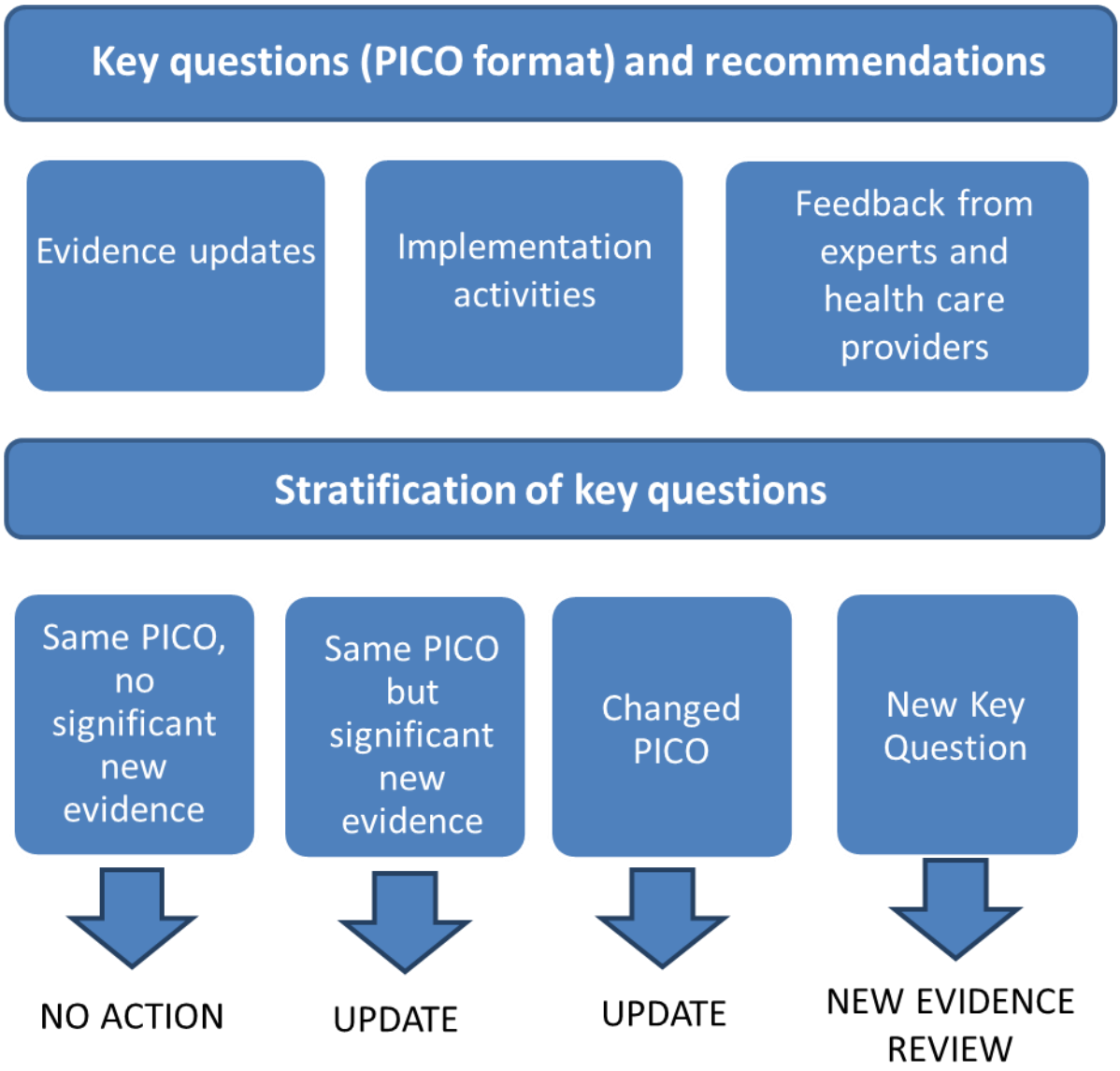
Based on the review process, the key questions issued in 2010 were stratified into one of the following four categories (see Figure 1):

- same population, intervention, comparison and outcome (PICO), no significant new evidence: no change;

- same PICO but significant new evidence: update existing evidence profile and recommendation;
- changed PICO: update existing evidence profile and recommendation;
- new key question, new PICO: draft new evidence profile and recommendation.

In consultation with the Guideline Development Group (GDG), the key questions were then finalized for evidence review and synthesis process. No modification of the overall scope of the guidelines was done after initial approval of the update plan by the WHO Guideline Review Committee. Based on the feedback of GDG members and according to evidence availability and programmatic experience, the key questions were further refined.

Figure 1. Flow chart describing the process followed to identify key questions and recommendations to be updated, and new key questions to be developed



Guideline update methodology

The mhGAP 2015 guideline update compiles 29 evidence-based recommendations for the following priority MNS disorders: depression, psychosis and bipolar disorders, epilepsy and seizures, child and adolescent mental disorders, dementia, alcohol use disorders, drug use disorders and self-harm and suicide.

The guideline development process followed the methods outlined in the WHO Handbook for Guideline Development[7]. The evidence quality assessment was conducted following GRADE methodology, where applicable. For each of the included key questions, an evidence profile was constructed summarizing the evidence retrieved, the GRADE quality assessment and discussion of values, preferences, benefits, harms and feasibility. The recommendations were then finalized by the GDG considering all of the above criteria.

Group process

WHO Guideline Secretariat

In order to oversee the guideline update process and evidence synthesis, WHO's Department of Mental Health and Substance Abuse coordinated the process of guideline development. In addition, other relevant WHO departments were consulted to advise and give feedback on the guideline development process (see Acknowledgment section).

Guideline Development Group

The Guideline Development Group (GDG) was convened to advise on the content and process, interpretation of evidence and to formulate and finalize the recommendations. The GDG included experts with multidisciplinary expertise relevant to the guideline and with adequate regional and gender representation (see Appendix 1). Regular discussions with the GDG took place by email and conference calls. A GDG meeting was organized in December 2014 for the review of evidence and finalisation of recommendations.

Peer Reviewers

A group of experts from different disciplines and regions, identified by the WHO secretariat and the GDG, reviewed the key questions during the initial stages of the guideline update process and also reviewed the final evidence profiles commenting on the evidence review process, clarity and implications for implementations (see Acknowledgment section).

Declaration of Interest

Declarations of interest (DoI) were requested from GDG members, experts involved in the evidence review process and from peer reviewers. According to the WHO Handbook for Guideline Development, interests were reviewed as per the following categories: financial (any income or support that is related to, or could be affected by, the outcome of this guideline update) and academic and public positions (any interest that could be reasonably perceived to affect an individual's objectivity and independence while working on this guideline update). The following possibilities were foreseen: (a) the conflict of interest requires no action

[7] World Health Organization. WHO handbook for guideline development – 2nd edition. World Health Organization, Geneva, Switzerland, 2014.

beyond declaration at the meeting and reporting in the final guideline; (b) the conflict of interest is significant but related to only some areas of the GDG work in which case the participant will not participate when the group considers these areas and will not have access to the relevant documents; (c) the conflict of interest is such that participation in the discussion is appropriate, but the member will be recused for development and ratification of recommendations; or (d) the conflict of interest is such as to preclude participation.

Managing Conflict of Interest

The WHO secretariat noted any potential financial, academic and positional conflicts of interest and summarized these. In the case of a conflict of interest among GDG members, the WHO secretariat decided whether and to what extent the person could participate in the guideline development. GDG members declared potential conflicts of interest in their forms. A 'Note for the Record' was developed following consultation with the Director of the Department (see Appendix 2). The overview of declarations can be found in Appendix 3). At the GDG meeting in December 2014, the information on declaration of interest was presented as per the Note for the Record, and GDG members were given the opportunity to comment or express concern about declared interests of another group member. No further comments were received.

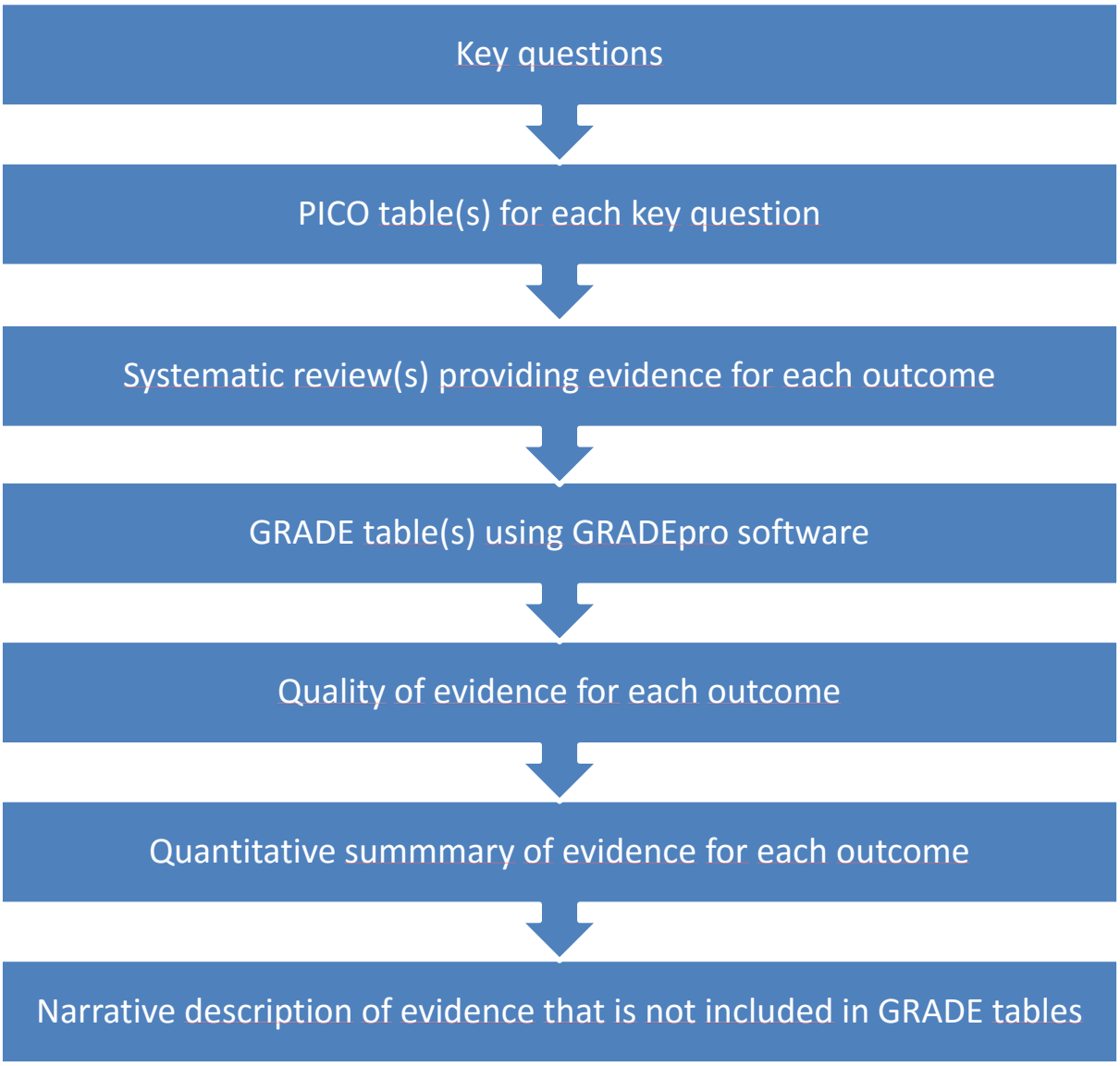
Evidence synthesis

The evidence profiles and GRADE tables were developed according to the following process:

- The PICO questions were defined as previously described. The outcomes were selected and prioritized by WHO Secretariat in consultation with the GDG members.
- The search strategy for each evidence profile was developed, in consultation with WHO librarian or other experts in information retrieval. Comprehensive searches of major bibliographic databases (see Appendix 4) were conducted in order to identify one or more systematic review(s) that match the PICO terms. When possible, high-quality and recent systematic reviews were used to draft evidence profiles. If only low-quality or not recent systematic reviews were identified, new systematic reviews were commissioned.
- The evidence retrieval and synthesis was carried out as per the WHO Handbook for Guideline Development (see Figure 2).
- The evidence profiles were developed according to the following structure:
    - Background information
    - Information on PICO (Population/ Intervention / Comparison / Outcome)
    - Search strategy
    - Summary table of evidence used as per the PICO
    - Narrative description of studies included in the analysis
    - GRADE tables (or other presentation of quality assessment if GRADE was not possible, e.g. in case of pharmacokinetic data)
    - Additional evidence not included in GRADE tables
    - Summary of evidence
    - Evidence to recommendation table

All evidence profiles can be found in Annex 1.

Figure 2. From key questions identified requiring an update to evidence profiles: flow-chart describing the process to identify, summarize and rate the evidence for each key question



The quality assessment was conducted according to the GRADE methodology[8]. This considered study design (Randomized Controlled Trial [RCT] or observational studies), risk of bias, inconsistency, indirectness, imprecision and risk of reporting bias. The quality of evidence for each intervention was graded as high, moderate, low or very low according to the considerations listed. Quality of evidence is defined as the extent to which one could be confident that an estimate of effect or association was correct. The implications of these categories are detailed in Table 1. Guiding principles describing how to assess each of the criteria of the GRADE methodology were prepared in advance and provided to technical experts (see Appendix 5), to

[8] The GRADE methodology can be found at **http://www.gradeworkinggroup.org/index.htm**

ensure transparency and consistency across all evidence profiles. All GRADE tables are included in their respective evidence profile.

Table 1. The quality of evidence in GRADE

Level of evidence	Rationale
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 the effect.

WHO Handbook for Guideline Development, 2nd edition 2014

Translating evidence into recommendations

The 'Evidence to recommendation table' was included in the evidence profiles capturing benefits and/or harms, quality of evidence, values and preferences, feasibility, and the recommendation and remarks. The GDG considered benefits, harms, values, preferences and feasibility for developing the recommendation and its strength.

Evidence on Benefits and Harms

The evidence on benefits and harms was summarized based on the review and synthesis process including the GRADE tables, along with the presentation of the quality of evidence.

Values and Preferences

This section details issues that may give rise to preferences in favour of or against the intervention among those affected by the recommendation. Some of the values and preferences that were considered during the preparation of the evidence profiles and during the discussion with the GDG panel included:

- Protection of human rights and dignity (e.g., interventions that are sometimes provided on a non-voluntary basis)
- Prevention of discrimination (and stigma)
- Prevention of medicalization of social problems
- Promotion of individual and family members' capacity and skills

Values and preferences information was based on the expert knowledge of GDG members, external expert reviewers and other technical experts.

Feasibility

This section considered the issues around feasibility and resource use based on GDG members and experts knowledge and experience from implementation of the guideline, especially in LAMICs. Some of the

feasibility issues that were considered during the development of the evidence profiles, during GDG discussion and while drafting and finalising the recommendations and accompanying remarks included:

- Inclusion in the WHO Essential Medicines List and likely availability of medication in LAMICs
- Acquisition cost
- Availability of adequately trained health care providers in LAMIC for delivery of this intervention
- Specific training requirements
- Specific laboratory requirements
- Other equipment requirements
- Continuous supply of medication (comment if sudden disruption of supply could have harmful consequences, e.g., for anti-epileptics)
- Specific supervision requirements

Strength of recommendation

The strength of a recommendation expresses the degree to which the GDG is confident in the balance between the desirable and undesirable consequences of implementing the recommendation. When the GDG was very certain about this balance (i.e. the desirable consequences clearly outweigh the undesirable consequences), it issued a strong recommendation in favour of an intervention. When it was uncertain about this balance, however, it issued a conditional recommendation. The table below based on the WHO Handbook for Guideline Development provides an aid to interpreting the strength of a recommendation.

Audience	**Strong recommendation**	**Conditional recommendation**
Patients	Most individuals in this situation would want the recommended course of action; only a small proportion would not.	Most individuals in this situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the intervention.	Different choices will be appropriate for individual patients, who will require assistance in arriving at a management decision consistent with his or her values and preferences.
Policymakers	The recommendation can be adopted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

In some cases the GDG proposed a strong recommendation even with low quality of evidence if the benefits of the intervention significantly outweighed the harms associated with the intervention or if there were strong values and preferences or because of feasibility of implementation. For example, if the quality of the evidence for an intervention is low, but not using the intervention could lead to the death of the patient, a strong recommendation was made. The rationale for the recommendations is included in the evidence profile with regards to the clinical evidence, values and preferences and feasibility.

GDG meeting

The GDG meeting was held in Geneva, Switzerland in December 2014 with the aim to reach consensus on the mhGAP Guideline update recommendations. The evidence profiles were reviewed and discussed in detail. During the meeting, the GDG members considered the following:

i. Summary and the quality of the available evidence on benefits and harms
ii. Values, preferences and feasibility issues related to the recommended interventions in different settings
iii. The resource use implications of options available, mainly considering the perspectives of programme managers in low-resource settings

Decision-making process

The decision-making process proposed was the following: After discussion, GDG members would reach an agreement on each recommendation based on the draft prepared by the WHO Secretariat. In the event of disagreements, the chair(s) and methodologist(s) would ascertain whether the disagreement is primarily related to the interpretation of data or the formulation of the recommendation. Draft recommendations would be revised accordingly in order to achieve unanimous agreement. If unanimous agreement was not reached, GDG members would vote on revised draft recommendations. Voting would be executed by raising hands. GDG members would have the option of having their objection recorded. In case of voting, consensus would be considered as the majority agreement of the guideline group members. WHO staff members present at the meeting, as well as other external technical experts involved in the collection and review of the evidence would not be allowed to vote.

Unanimous agreement by discussion was reached by GDG on all the recommendations and their rating and therefore, no voting was required.

External peer review

The evidence profiles were circulated to external peer reviewers to comment on the clarity of the language and possible implications of the recommendations. The comments on each evidence profile were considered by the WHO Secretariat and GDG and incorporated as per the scope of each of the key questions included in the guideline update process.

Publication, dissemination and evaluation of the guideline

Presentation of the updated mhGAP guideline

The updated mhGAP guideline will be made available in the “mhGAP Evidence Resource Centre”, a dedicated internet space on the WHO website where guideline materials can be found organized according to mhGAP priority condition: http://www.who.int/mental_health/mhgap/evidence/en/. From the Evidence

Resource Centre, all the evidence profiles can be accessed with detailed information on available evidence, GRADE quality analysis, narrative descriptions of the evidence that was not inserted into GRADE tables and considerations on values and preferences and feasibility issues.

Subsidiary products

The mhGAP guideline is developed in English: however, mhGAP products (which are derived from the guideline, including the mhGAP-intervention guide and training materials) will be developed and translated into other WHO official languages (depending upon availability of funding) for wider dissemination, and in collaboration with WHO Regional Offices.

The updated mhGAP guideline will be incorporated into an updated version of the *mhGAP Intervention Guide (mhGAP-IG) for mental, neurological and substance use disorders in non-specialized health settings (version 2.0)*. The mhGAP-IG translates the evidence-based recommendations into simple clinical protocols and algorithms to facilitate decision-making for clinical assessment and management. It is aimed at non-specialist health-care providers working at first- and second-level facilities. It is important that they are trained and then supervised and supported by specialists. The mhGAP-IG is also aimed for health care planners and programme managers in close conceptual and strategic synergy with the WHO's Comprehensive Mental Health Action Plan 2013-2020. The updated mhGAP guideline will be similarly incorporated into other mhGAP implementation materials.

Dissemination plans

Relevant departments in Ministries of Health will be notified of the guideline through WHO Regional and Country Offices. A briefing package will be prepared for technical officers outside of WHO Headquarters that will include an executive summary and "Q&A" related to policy and programme implications. In particular, the briefing will highlight the new changes in the specific recommendations of the guideline.

Capacity building activities will be undertaken through regional and sub-regional meetings and other activities related to mhGAP and Comprehensive Mental Health Action Plan implementation.

Supporting local adaptation and implementation

Local adaptation is necessary to ensure that the most burdensome conditions in a given country are covered and that the mhGAP guideline is appropriate for the local conditions that affect the care of people with MNS disorders. Adaptation includes language translation and ensuring that the interventions are acceptable in the local socio-cultural context and suitable for the local health system.

The implementation of the mhGAP guideline will also be supported locally through the adoption of the Comprehensive Mental Health Global Action Plan at country level. The national capacity building process will

also be supported through collaboration with other partners such as other international organizations and civil society partners.

Monitoring and evaluating quality of the guideline

After the publication of this guideline update, WHO will continue to collect regular feedback from implementation activities in order to evaluate its usefulness and impact. WHO will additionally continue to collect feedback from international experts and health care providers 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.

Future review and update

The WHO Department of Mental Health and Substance Abuse will regularly monitor new evidence in these areas with the assistance of a WHO Collaborating Centre. The Department will also collect regular feedback from country implementation teams on mhGAP products, which are based on the mhGAP guideline.

After two years, literature searches will be carried out to check whether there are any major changes in the literature of any of the areas covered by the guideline. This will identify new potentially relevant evidence and enable us to assess whether the new information might have a significant effect on the recommendations. As two-yearly monitoring will need to be affordable and feasible in the long-term, this is not based on full literature reviews, but will consist of scoping searches of systematic reviews and other secondary products such as other evidence-based guidelines. Evidence profiles will be complemented with a short (up to one page) overview of how new evidence may affect the recommendation.

We plan to update the guideline again in five years using similar methodology to that of this second edition.

List of Recommendations and Remarks

The recommendations for the mhGAP Guideline Update are provided below, including quality of evidence, strength of recommendation and remarks. These recommendations have been developed following the WHO Guideline Development process. Definition and description of interventions, together with the evidence retrieved and analysis of values and preferences and feasibility issues leading to these recommendations can be found in individual evidence profiles. These should be read in addition to the other relevant recommendations of the mhGAP guideline (available through the mhGAP Evidence Resource Centre: http://www.who.int/mental_health/mhgap/evidence/en/).

mhGAP Priority Condition: Depression

DEP1: Antidepressant medication in comparison with psychological treatment for moderate-severe depressive disorder *[New 2015]*

Recommendation

As first-line therapy, health care providers may select psychological treatments (such as behavioural activation [BA], cognitive behavioural therapy [CBT], or interpersonal psychotherapy [IPT]) or antidepressant medication (such as selective serotonin reuptake inhibitors [SSRIs] and tricyclic antidepressants [TCAs]). They should keep in mind the possible adverse effects associated with antidepressant medications, the ability to deliver either intervention (in terms of expertise, and/or treatment availability), and individual preferences.

Quality of Evidence: Low

Strength of recommendation: Conditional

Rationale:

Although the quality of the evidence is low to very low, the benefits of either intervention outweigh their harms with no differences between the interventions in direct comparisons. Indirect comparisons suggest that adverse effects are likely more pronounced with antidepressant medications.

Remarks:

Sufficient human resources (e.g., community health workers trained and supervised in delivering psychological treatment) and continuous medication supply need to be made available for psychological and antidepressant treatment, respectively.

Health care providers should discuss with help-seekers the pros and cons of either treatment (e.g. effects, including side effects, and time needed) allowing the person to decide which treatment he or she prefers.

DEP2: Comparative effectiveness of different formats of psychological treatments for depressive disorder *[New 2015]*

Recommendation

Health care providers can offer different treatment formats of WHO's recommended, structured psychological interventions for adults and older adolescents with depressive disorder. These include behavioural activation, cognitive behavioural therapy (CBT), interpersonal psychotherapy (IPT), problem-solving treatment as an adjunct treatment (e.g. in combination with antidepressants). Different treatment formats for consideration include (a) individual and/or group face-to-face psychological treatments delivered by professionals and supervised lay therapists, as well as (b) self-help psychological treatment.

While face-to-face psychological treatment or guided self-help psychological treatment are likely to have better outcomes than unguided self-help, the latter may be suitable for those people who either (a) do not have access to face-to-face psychological treatment or guided self-help psychological treatment or (b) are not willing to access such treatments.

Quality of Evidence: Low

Strength of recommendation: Conditional

Rationale:

There is low-quality evidence suggesting that the difference between individual and group treatment is small or non-existent. With respect to face-to-face versus self-help treatment, the research is more extensive, but the quality is very low. Overall there is substantial certainty in the value of expanding care through different means, and in the feasibility of expanding the delivery of psychological interventions beyond care by mental health professionals.

Remarks:

Choice of treatment format depends on social and health systems context.

WHO-recommended structured psychological treatments for depressive disorders in adults include: behavioural activation (BA), cognitive behavioural therapy (CBT) and interpersonal psychotherapy (IPT). In addition, existing WHO-recommended structured brief psychological treatments include problem-solving treatment as an adjunct treatment (e.g., in combination with antidepressants) for depressive disorder.

WHO recommended structured psychological treatments for emotional disorders in adolescents include: cognitive behavioural therapy, interpersonal psychotherapy, and caregiver skills training.

Self-help psychological treatment may involve information-technology (IT) supported self-help materials and paper-based self-help books.

mhGAP Priority Condition: Psychosis (including schizophrenia and bipolar disorder)

PSY1: Role of depot antipsychotic medication in long-term antipsychotic treatment *[Updated 2015]*

Recommendation

In people with psychotic disorders (including schizophrenia) requiring long-term antipsychotic treatment, depot antipsychotics can be offered instead of oral medications as part of a treatment plan.

Quality of Evidence: Very low

Strength of recommendation: Conditional

Rationale:

Although the quality of the evidence is low to very low, the benefits of depot versus antipsychotics are similar in terms of hospitalizations and dropouts due to inefficacy. In terms of long-term relapse prevention, there is evidence that depot antipsychotics are significantly more effective than oral antipsychotics. The evidence also suggests that depot antipsychotics do not differ in terms of dropouts for adverse events when compared to oral preparations.

Remarks:

Patients and carers should be offered clear and accessible information in a suitable format regarding the use and possible side effects of oral versus depot preparations.

PSY2: Antipsychotics and mood stabilizers (lithium, valproate, or carbamazepine) for maintenance treatment of bipolar disorder *[Updated 2015]*

Recommendation

Lithium or valproate or certain second-generation antipsychotics (*aripiprazole, olanzapine, paliperidone extended release, quetiapine, and risperidone long acting injection release)* can be offered for the maintenance treatment of bipolar disorder. If treatment with one of these agents is not feasible, first-generation antipsychotics or carbamazepine may be used. Maintenance treatment should be offered in primary health care settings under supervision of a specialist.

Quality of Evidence: Low

Strength of recommendation: Conditional

Rationale:

Although there are concerns about safety and tolerability associated with long-term treatment with antipsychotics

and mood stabilizers, there is low-quality evidence suggesting that the benefits of lithium, valproate and certain second-generation antipsychotics outweigh their harms. In terms of tolerability, both lithium and valproate have a narrow therapeutic index and can be toxic to multiple organ systems. A further important issue is the burden of taking mood stabilizers that requires regular blood monitoring.

Remarks:

Treatment with lithium should be initiated only in those settings where personnel and facilities for close clinical and laboratory monitoring are available.

All studies evaluating antipsychotic treatments have investigated the efficacy and tolerability profile of second-generation antipsychotics, while no direct evidence is available for first-generation antipsychotics. Evidence was considered for certain second-generation antipsychotics (aripiprazole, olanzapine, paliperidone extended release, quetiapine, and risperidone long acting injection release).

PSY3: Recovery-oriented psychosocial strategies enhancing independent living and social skills (such as life skills and social skills training) [2015]

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Recommendation

Recovery-oriented psychosocial interventions (e.g., life skills training, social skills training) to enhance independent living skills can be offered for people with psychotic disorders (including schizophrenia and bipolar disorder) and for their families and/or caregivers.

Facilitation of assisted living, independent living and supported housing that is culturally and contextually appropriate may be considered as an option for people with psychotic disorders (including schizophrenia and bipolar disorder). Careful consideration should be given to the functional capacity and the need for stability and support when advising and facilitating optimal housing arrangements.

Quality of Evidence: Very low

Strength of recommendation: Conditional

Rationale:

Randomized evidence supporting the efficacy of recovery-oriented psychosocial interventions is sparse and inconclusive. However, findings from a number of observational studies carried out in a very diverse range of settings suggest that benefits outweigh the harms. Overall there is substantial certainty in the value of psychosocial interventions, which may improve the social inclusion of people with psychotic disorders, as well as family members and caregivers, while reducing disability and preventing human rights violations.

Remarks:

Life skills training is a recovery oriented psychosocial intervention that emphasises the needs associated with independent functioning, and is usually part of the rehabilitation process. Social skills training is a recovery oriented psychosocial interventions included in illness management programs aimed at recovery.

Facilitation of assisted living and supported housing can act as a base from which people with severe mental disorders can achieve numerous recovery goals. Different housing strategies can be adopted depending on local resources and local cultural norms. Normal housing (single or shared, if acceptable to the user) or group living alternatives with appropriate support from a specialist may be crucial in promoting recovery in people with mental disorders.

Users, their families/caregivers and the community should be involved in the design, implementation and evaluation of these psychosocial interventions, in coordination with health and social professionals. Professionals delivering psychosocial interventions should have an appropriate level of competence and, wherever possible, be regularly supervised by the relevant specialists. Psychosocial interventions should be continued as long as needed by the user and his/her family and therefore should be planned and developed in a sustainable way.

PSY4: Recovery-oriented strategies enhancing vocational and economic inclusion (such as supported employment) [2015]

Recommendation

Recovery-oriented strategies enhancing vocational and economic inclusion (e.g. supported employment) can be offered for people with psychosis (including schizophrenia and bipolar disorder). Such strategies should be contextualised to their social and cultural environment, using formal and non-formal recovery-oriented interventions that may be available, and using a multisectoral approach.

Quality of Evidence: Low

Strength of recommendation: Conditional

Rationale:

Randomized evidence supporting the efficacy of recovery-oriented strategies enhancing vocational and economic inclusion is sparse and inconclusive. However, findings from a number of observational studies carried out in a very diverse range of settings suggest that benefits outweigh the harms. Overall there is substantial certainty in the value of recovery-oriented strategies enhancing vocational and economic inclusion, which may improve the social inclusion of people with psychotic disorders, as well as family members and caregivers, while reducing disability and preventing human rights violations.

Remarks:

Non-specialist health care providers should facilitate opportunities for people with psychosis and their families/caregivers to be included in economic activities in real world settings. Implementation of recovery-oriented psychosocial intervention programs requires a multisectoral approach such as collaboration with housing, employment, education and social sector.

PSY5: Second-generation antipsychotic medications for psychotic disorders (including schizophrenia) [New 2015]

Recommendation

Second-generation antipsychotics (with the exception of clozapine which is indicated for treatment resistant psychosis) can be offered for the treatment of psychotic disorders (including schizophrenia). There is no clinically relevant advantage of one second-generation antipsychotic over others and choice should be based on availability, cost, patient preferences and possible adverse effects associated with each medication.

Quality of Evidence: Low

Strength of recommendation: Conditional

Rationale:

Although the quality of the evidence is low, the benefits of second-generation antipsychotics outweigh their harms with no clinically relevant differences between individual interventions in direct comparisons. In the long-term, there are safety and tolerability concerns associated with antipsychotic treatment. A feasibility issue is the burden of taking medicines that require regular clinical and laboratory monitoring.

Remarks:

Although clozapine is more effective than other second-generation antipsychotics, its use is limited to patients that have not responded to other antipsychotics, as it may cause agranulocytosis. Regular blood tests during treatment are required to decrease this risk. Without monitoring, agranulocytosis occurs in about 1% of patients who take clozapine during the first few months of treatment.

The second generation antipsychotics considered in this evidence profile are aripiprazole, asenapine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, ziprasidone, zotepine. Possible adverse effects include sedation, metabolic, extrapyramidal, cardiovascular and hormonal side-effects.

PSY6. Pharmacological interventions in adolescents with psychotic disorders *[New 2015]*

Recommendation

In adolescents with psychotic disorders (including schizophrenia and bipolar disorder) certain second-generation antipsychotic medications (aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone) can be offered as a treatment option under supervision of a specialist.

If treatment with one of the above agents is not feasible, first-generation antipsychotics (haloperidol, chlorpromazine, perphenazine, molindone) may be used under supervision of a specialist.

Quality of Evidence: Very low

Strength of recommendation: Conditional

Rationale:

Although the quality of the evidence is very low, the benefits of certain second-generation antipsychotics outweigh their harms with no clinically relevant differences between individual interventions in direct comparisons. Some first-generation antipsychotics may be similarly effective in comparison with second-generation antipsychotics. In the long-term, there are relevant safety and tolerability concerns associated with antipsychotic treatment in this age group. A feasibility issue is the burden of taking medicines that require regular clinical and laboratory monitoring.

Remarks:

All studies in adolescents with psychotic disorders (including schizophrenia and bipolar disorder) have investigated the efficacy and tolerability profile of second generation antipsychotics, while no direct evidence is available for first-generation antipsychotics. However, comparisons of second-generation versus first-generation antipsychotics in adolescents and indirect evidence collected in adults with psychotic disorders (including schizophrenia and bipolar disorder) demonstrated the efficacy of first-generation antipsychotics.

Antipsychotic medications can give rise to adverse effects.

The evidence for the use of antipsychotics in adolescents is limited to specialist service settings and does not follow patients over long periods of time. It is for these reasons that supervision is required and that patients are monitored regularly for any incidence of unwanted side effects.

As there is no clinically relevant advantage of one antipsychotic over the others, choice should be based on availability, cost, preferences and possible negative consequences associated with each medication, including sedation, metabolic, extrapyramidal, cardiovascular and hormonal side-effects.

mhGAP Priority Condition: Epilepsy

EPI1: Anti-epileptic medications for management of acute convulsive seizures when no intravenous access is available [Updated 2015]

Recommendation

When intravenous access is not available for the control of acute seizures in adults, non- parenteral routes of benzodiazepine administrations should be used. Options include rectal diazepam, buccal or intranasal midazolam, rectal or intranasal lorazepam. The preference may be guided by availability, expertise and social preference. Some benzodiazepines (lorazepam or midazolam) may be given by intramuscular route, which requires additional expertise. Intramuscular administration of diazepam is not recommended because of erratic absorption.

Quality of Evidence: Low

Strength of recommendation: STRONG

Rationale:

A strong recommendation was made even with low quality evidence because the risk associated with not attempting to control seizures (e.g., sequelae of prolonged seizure or death) far outweighs any harms associated with using the interventions recommended. Although the quality of the evidence is low, there is no clinically important difference between non-intravenous routes of administration of benzodiazepines compared to intravenous routes for management of acute convulsive seizures. In a convulsing child or adult, establishing an intravenous access may be difficult; there may be lack of trained health care workers and lack of equipment in resource-limited settings. For patients and their families, non-intravenous treatment options may increase patient and family satisfaction. The availability of non-parenteral formulations of benzodiazepines may be a feasibility issue.

Remarks:

Relevant scenarios for using non-intravenous formulations may include community settings (pre-hospitalisation) or in a health care facility that is not equipped to administer intravenous medications or which does not have trained health care workers.

Intravenous formulations can be used for non-intravenous administration routes. If this should occur, particular caution should be taken with dosages to avoid administration errors.

EPI2: First-line anti-epileptic medication for management of acute convulsive seizures, when intravenous access is available *[2015]*

Recommendation

In adults presenting with acute convulsive seizures where intravenous access is available, either intravenous lorazepam or diazepam can be administered to terminate the seizure. Intravenous lorazepam (if available) may be preferred over intravenous diazepam because of slightly superior benefit-risk profile.

Quality of Evidence: Low

Strength of recommendation: Conditional

Rationale:

Although the quality of the evidence is low, the benefits of anti-epileptic medications outweigh their harms with intravenous lorazepam appearing to be more effective than intravenous diazepam for management of acute convulsive seizures in adults. Control of acute convulsive seizures is of critical importance as they are associated with substantial morbidity and mortality. Both intravenous lorazepam and diazepam are included in WHO Model Essential Medicine List.

Remarks:

Intravenous lorazepam may not be available in many low-and middle-income country settings.

In field settings, where the environmental temperatures are high and refrigeration is not available, intravenous diazepam may be preferable over lorazepam because of its better stability at higher environmental temperatures.

No recommendation can be made regarding intravenous midazolam, phenobarbital and phenytoin due to insufficient evidence.

EPI3: Anti-epileptic medications for management of established status epilepticus *[Updated 2015]*

Recommendation

In adults with established status epilepticus, i.e. seizures persisting after two doses of benzodiazepines, either intravenous valproic acid, intravenous phenobarbital or intravenous phenytoin can be used with appropriate monitoring.
Intravenous valproic acid is preferred over intravenous phenobarbital or intravenous phenytoin because of its superior risk-benefit profile. The choice of these medications depends on local resource settings, including availability and facilities for monitoring.
Where intravenous infusion may not be feasible, intramuscular phenobarbital remains an option, with appropriate monitoring. Phenytoin and valproic acid should not be given intramuscularly.

Quality of Evidence: Very low

Strength of recommendation: Conditional

Rationale:

Status epilepticus is a medical emergency associated with substantial mortality and so its control is of critical importance. Although the quality of the evidence is very low, the benefits of intravenous phenytoin, phenobarbital and valproic acid outweigh their harms with no clinically relevant differences between individual interventions in direct comparisons in management of established status epilepticus. Advantages of valproic acid include lesser risk of cardiorespiratory side effects. Valproic acid is a broad-spectrum medication active against all types of seizures,

and hence may be a good agent for maintenance therapy after the acute control of seizures in idiopathic generalized epilepsy or when the type of seizure/ epilepsy syndrome is not clear. However, valproic acid has the risk of hepatotoxicity and pancreatitis. Phenobarbital carries the risk of sedation and respiratory depression, which may be increased if it is used after benzodiazepines. Phenytoin carries the risk of arrhythmia and hypotension and difficulties in administration.

Remarks:

The above medications are initiated when seizures persist after two doses of benzodiazepines.

The choice of the medication can be affected by a number of factors, for example, the availability, cost and side effect profile of each.

EPI4: Anti-epileptic medications for adults and children with HIV *[New 2015]*

Recommendation

In comparison with enzyme-inducing anti-epileptic medications (phenobarbital, phenytoin, carbamazepine) or valproic acid, newer generation anti-epileptic medications that are not hepatically metabolized (i.e. leviteracetam, lacosamide, topiramate, gabapentin and pregabalin) may be preferred to use in people with HIV on certain antiretroviral medications (protease inhibitors or non-nucleoside reverse-transcriptase inhibitors).

If the treatment with newer generation anti-epileptic medications is not feasible, valproic acid is preferred over the enzyme-inducing anti-epileptic medications (phenobarbital, phenytoin, and carbamazepine). In all cases, close monitoring of HIV viral load and regular clinical monitoring is required. If resources are available, anti-epileptic medication levels should be monitored.

Quality of Evidence: Very low

Strength of recommendation: Conditional

Rationale:

HIV and epilepsy comorbidity is common and presents a clinical challenge, thus in HIV-positive patients requiring antiepileptic medications and who are also on antiretroviral medications, the optimal choice must be considered based on the risk of drug-drug interactions and effects on HIV viral suppression. Although the quality of the evidence is very low, newer antiepileptic medications and valproic acid may provide useful alternatives to first-generation agents. A feasibility issue is that the newer antiepileptic medications are not on the WHO Essential Medicine List and so are more expensive. In addition, facilities for routine antiepileptic drug level monitoring are either not available or can be expensive in many countries.

Remarks:

Further research is needed in the following areas:

- Safety and efficacy of newer generation anti-epileptic medications (e.g., levetiracetam, lamotrigine, , topiramate, pregabalin, and gabapentin) in patients on antiretroviral medications

- Clinical adverse effects in patients on antiretrovirals and anti-epileptic medications

- Further studies on the effects of hypoalbuminemia, hypergammaglobulenemia, and decreased gastrointestinal absorption on anti-epileptic medication levels in HIV-positive patients

- Interaction studies and safety and efficacy studies in children on anti-epileptic medications and antiretrovirals

EPI5: Anti-epileptic medicines for medication resistant convulsive epilepsy *[New 2015]*

Recommendation

Certain newer anti-epileptic medications (lamotrigine, levetiracetam and topiramate) should be offered as add-on therapy in patients with medication resistant convulsive epilepsy.

The essential anti-epileptic medications (carbamazepine, phenobarbital, phenytoin, and valproic acid) may be of benefit as add-on therapy in patients with medication resistant convulsive epilepsy.

Quality of Evidence: Moderate

Strength of recommendation: Conditional

Rationale:

The balance of benefit versus harms is in favour of treatment with newer antiepileptic medications in medication-resistant convulsive epilepsy. The evidence for essential antiepileptic medications as an add-on therapy was based on observational studies. There were no head-to-head studies comparing the efficacy of the essential anti-epileptic medications and the newer anti-epileptic medications of interest against each other for adults and children with medication resistant convulsive epilepsy. Despite the fact that anti-epileptic medications are associated with some adverse events, most people with medication-resistant convulsive epilepsy would choose to be on these medications to decrease the risk of morbidity and mortality. The newer antiepileptic medications are not on the WHO Essential Medicines List and so cost may prove a barrier to use in low-resource settings.

Remarks:

Medication selection should also be appropriate based on the type of epilepsy as some anti-epileptic medications can worsen generalized convulsive seizures (e.g., carbamazepine, phenytoin and phenobarbital should be avoided in patients with myoclonic epilepsy). Patients' comorbidities and childbearing potential also have to be considered when recommending a newer antiepileptic medication in those with medication resistant convulsive epilepsy as some antiepileptic medications are associated with a higher risk of teratogenicity and worst neurodevelopmental outcomes than others (e.g., valproic acid), or could worsen comorbid conditions (e.g., depression, obesity, etc.).

mhGAP Priority Condition: Mental disorders with childhood onset

CH1: Caregiver skills training for management of developmental disorders *[Updated 2015]*

Recommendation

Caregiver skills training should be provided for management of children and adolescents with developmental disorders, including intellectual disabilities and pervasive developmental disorders (including autism).

Quality of Evidence: Low

Strength of recommendation: Strong

Rationale:

A strong recommendation was made even with low quality evidence based on the benefits outweighing harms and the values and preferences indicating that children and adolescents with intellectual disabilities or pervasive developmental disorders have the right to a supportive and understanding family environment. Low-quality evidence suggests that caregiver skills training is associated with better outcomes in child development and reductions in problem behaviours. It is generally agreed that it is important for caregivers to acquire skills to better enable and support the development, functioning and participation of children with developmental disorders. In terms of feasibility, evidence supports the notion that training for caregivers of children and adolescents with intellectual disabilities and pervasive developmental disorders can be effectively delivered by non-specialists in community settings.

Remarks:

Caregiver skills training should use culturally appropriate training material relevant for those disorders to improve development, functioning, and participation of the children and adolescents within families and communities.

Health-care providers need additional training to be able to offer caregiver skills training.

Training and education of caregivers and other family members could ensure that children with intellectual disabilities or pervasive developmental disorders are given the dignity and opportunities that they are entitled to.

CH2: Psychosocial interventions for treatment of behavioural disorders *[Updated 2015]*

Recommendation

Behavioural interventions for children and adolescents, and caregiver skills training, may be offered for the treatment of behavioural disorders.

Quality of Evidence: Low

Strength of recommendation: Conditional

Rationale:

The available evidence indicates that caregiver skills training and behavioural interventions for the patients can reduce symptoms for children with behavioural disorders and improve family and caregiver functioning. Additionally, behavioural and cognitive behavioural interventions can be effective in improving school performance. There were no adverse outcomes reported, in terms of additional psychological or familial burdens associated with participation in these interventions. There is value of intervening early to reduce adverse outcomes associated with behavioural disorders.

Remarks:

The choice of behavioural intervention (eg. behavioural and cognitive behavioural therapies, school-based therapies, and caregiver skills training), and how it is implemented should be based on the type of behavioural disorder(s) and the age and developmental stage of the child or adolescent. The child or adolescent's family should be involved in the intervention whenever appropriate. The content should be culturally sensitive and should not allow violation of the child or adolescent's basic human rights according to internationally endorsed principles.

The social environment, family context and other psychosocial and physical risk factors that may be contributing to or exacerbating the behaviour disorder should be considered and addressed, whenever possible.

Health care providers should be aware that behavioural problems may be an expression of underlying emotional problem(s)/disorder(s).

CH3: Psychosocial interventions for treatment of emotional disorders *[Updated 2015]*

Recommendation

Psychological interventions, such as cognitive behavioural therapy (CBT), interpersonal psychotherapy (IPT) for children and adolescents with emotional disorders, and caregiver skills training focused on their caregivers, may be offered for the treatment of emotional disorders.

Quality of Evidence: Low

Strength of recommendation: Conditional

Rationale:

For children with emotional disorders, there is low quality evidence that behavioural and cognitive behavioural interventions can lead to symptom reduction and disorder remission. There were no adverse outcomes reported, in terms of additional psychological or familial burdens associated with participation in these interventions. Feasibility depends on local resources, as well as the choice and format of the psychosocial treatment offered.

Remarks:

The choice of psychological intervention and how it is implemented should be based on the type of emotional problem(s) and the age and developmental stage of the child or adolescent. The child or adolescent's family should be involved in the intervention, whenever appropriate. The content should be culturally sensitive and should not allow violation of the child or adolescent's basic human rights according to internationally endorsed principles.

The social environment, family context, and other psychosocial and physical risk factors that may be contributing to or exacerbating the emotional disorder should be considered and addressed.

CH4: Antidepressants among adolescents with moderate-severe depressive disorder for whom psychosocial interventions have proven ineffective *[2015]*

Recommendation

When psychosocial interventions prove ineffective, fluoxetine (but not other Selective Serotonin Reuptake Inhibitors or Tricyclic Antidepressants) may be offered in adolescents with moderate-severe depressive episode/disorder. The intervention should only be offered under supervision of a specialist.

Quality of Evidence: Very low

Strength of recommendation: Conditional

Rationale:

Although in the long-term there are safety and tolerability concerns associated with antidepressant treatment in this age group, the evidence suggests that fluoxetine is an SSRI with a favourable benefit to risk ratio. Clinicians need to be trained in prescribing antidepressants, including side-effects monitoring.

Remarks:

Within the context of this recommendation, specialists include (a) psychiatrists and neuro-psychiatrists (b) paediatricians and family physicians with post-degree training in the management of adolescent depression.

The decision to prescribe fluoxetine should be made together with the adolescent in line with the evolving capacity of the adolescent.

Adolescents on fluoxetine should be monitored closely for suicide ideas/behaviour.

Fluoxetine treatment should not be started with greater than minimal effective doses. It is suggested to initiate treatment with 10 mg once daily and increase to 20 mg after 1 – 2 weeks (maximum dose 20 mg). If no response

in 6 – 12 weeks or partial response in 12 weeks, re-consult a specialist.

In countries that only have 20mg capsules that cannot be split in half, due to the long half-life of fluoxetine, it is possible to prescribe fluoxetine 20mg every other day (equivalent to initial dose of 10mg/day).

CH5: Effective strategies for detecting maltreatment of children and youth within the context of mental health and developmental assessment *[New 2015]*

Recommendation

Health care providers should be alert to the clinical features associated with child maltreatment and associated risk factors and assess for child maltreatment, without putting the child at increased risk.

Quality of Evidence: Very low

Strength of recommendation: Conditional

Rationale:

Evidence supporting the efficacy of strategies for detecting maltreatment of children and youth within the context of mental health and developmental assessment is sparse and inconclusive. No studies have evaluated the performance of measures in predicting referrals and health outcomes. However, it is generally agreed that it is important for health care providers to detect child maltreatment. It is recognised that assessment of child maltreatment requires a clinician who is competent enough to ask the right questions and to respond appropriately.

Remarks:

Inquiry into child maltreatment should occur in the context of case finding and diagnostic assessment by clinicians competent to do so and should be followed by interventions, referral and/or follow up. Inquiry and following actions should take into account the availability of interventions, such as caregiver skills training, and services. There is no evidence to support universal screening or routine inquiry.

The strategies, including reporting and follow-up of the assessment should be culturally sensitive and should not allow violation of children's basic human rights according to internationally endorsed principles.

Examples of child maltreatment include physical abuse, sexual abuse, neglect, emotional abuse and all other forms of child maltreatment.

CH6: Community-based rehabilitation for adults with developmental disorders including intellectual disabilities and autism spectrum disorders *[New 2015]*

Recommendation

Non-specialized health care providers can offer supporting, collaborating and facilitating referral to and from community based rehabilitation (CBR) programmes, if available, for care of adults with developmental disorders, including intellectual disabilities and pervasive developmental disorders (including autism).

Quality of Evidence: Very low

Strength of recommendation: Conditional

Rationale:

Evidence supporting the efficacy of community-based rehabilitation for adults with developmental disorders is sparse and inconclusive. The provision of psychosocial rehabilitation is in line with internationally endorsed principles on the rights of people with disabilities.

Remarks:

Intervention programmes should be developed and adapted taking into consideration the sociocultural context and with involvement of program users.

mhGAP Priority Condition: Dementia

DEM1: Cholinesterase inhibitors and memantine for treatment of dementia *[Updated 2015]*

Recommendation

Cholinesterase inhibitors and memantine may be offered to people with dementia in non-specialist health settings. Non-specialists need to be trained and supervised to ensure competence in diagnosis and monitoring.

The use of cholinesterase inhibitors should be focused upon those with mild to moderate Alzheimer's disease, where the majority of evidence is available.

Memantine may be considered for those with moderate to severe Alzheimer's disease and vascular dementia. Memantine should not be prescribed for Lewy Body dementia.

Quality of Evidence: Very low

Strength of recommendation: Conditional

Rationale:

Cholinesterase inhibitors and memantine offer symptomatic benefits in cognitive, functional, global and behavioural outcomes, although the size of this benefit is uncertain and the quality of the evidence very low. Adverse effects and safety in the long-term may represent serious concerns. Dementia diagnosis and subtype definition and management with the above medications require training, supervision and support. Moreover these medications are associated with high acquisition costs.

Remarks:

Consideration should be given to adherence and monitoring of adverse effects.

DEM2: Psychological therapies for people with dementia who have associated depression *[New 2015]*

Recommendation

People with dementia and mild to moderate symptoms of depression may be offered psychological interventions (such as cognitive behavioural therapy [CBT], interpersonal therapy [IPT], structured counselling and behavioural activation therapy), in non-specialized health care settings under supervision of a specialist.

Quality of Evidence: Low

Strength of recommendation: Conditional

Rationale:

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. There is limited low quality evidence that the use of psychological treatments may reduce symptoms of depression in this population. Delivery of these interventions require adequate training and supervision of non-specialist health care provider.

Remarks:

Psychological interventions may not be feasible as a treatment for people with severe dementia and symptoms of depression due to impaired cognitive function.

It is possible to train non-specialist health care workers to provide psychological treatments with the close supervision of a specialist.

None of the primary studies available on psychological interventions were carried out in low- or middle-income countries.

The type of psychosocial intervention offered should be based upon the capacity of health care workers and patient preferences.

DEM3: Pharmacological interventions (antidepressants) for people with dementia who have associated depression *[2015]*

Recommendation

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]) may be considered.

In people with dementia and mild to moderate depression, antidepressants should not be offered as a first-line treatment.

Quality of Evidence: Low

Strength of recommendation: Conditional

Rationale:

The evidence to support the use of antidepressants for the treatment of comorbid depression in dementia is inconclusive. Clinicians must be vigilant regarding the potential side-effects of antidepressants in this population, especially tricyclic antidepressants, as they are associated with side-effects that are potentially more problematic for elderly patients.

Remarks:

This evidence implies a need to change current practice of antidepressants being the first-line treatment of depression in individuals with dementia.

Tricyclic antidepressants (TCAs) are associated with more adverse effects than are selective serotonin reuptake inhibitors (SSRIs) in older adults.

DEM4: Oral nutrition supplementation or dietary education for caregivers for managing people with dementia at risk of undernutrition or currently undernourished *[New 2015]*

Recommendation

In people with dementia who are at risk of undernutrition, dietary advice aimed at food fortification should be tried first, and weight and nutritional status monitored. If nutritional status is not improved, then oral nutritional supplementation should be used (in the absence of any clinical contraindication) to achieve weight gain and restore nutritional status.

Quality of Evidence: Low

Strength of recommendation: STRONG

Rationale:

Undernutrition is common among people with dementia and is associated with significant adverse effects, including more rapid clinical progression and cognitive decline, hospitalization, falls and death. There is evidence that the use of oral nutritional supplementation is efficacious in attaining clinically significant weight gain in people with dementia who are undernourished or at risk of undernutrition, although the quality of the evidence is low. However oral nutritional supplementation is generally well tolerated among people with dementia and there is no evidence of any significant harms. Caregiver anxiety over their inability to achieve adequate nutrition and to stabilize the weight of the cared-for-person with dementia is a significant source of caregiver strain. A strong recommendation was made even with low quality evidence because the risk and negative health effects of malnutrition are serious and outweigh any harm that could be associated with the recommended treatment.

Remarks:

People with dementia should be regularly assessed for weight loss and nutritional status. For those who are found to be undernourished or at risk of undernutrition, an assessment should be carried out for general health status, dietary habits, and for the presence of any adverse feeding behaviours. Suspicion of serious underlying physical disease should trigger an urgent referral for medical assessment.

DEM5: Nutritional interventions for people with dementia or cognitive impairment *[New 2015]*

Recommendation

In people with either cognitive impairment or dementia, supplementation with nutrients, or use of Gingko biloba extracts should not be considered to improve cognitive function, to reduce the risk of developing dementia or to slow the progression of dementia once established.

When feasible, dietary deficiencies should be investigated and monitored in those with dementia and appropriate supplementations should be provided.

Quality of Evidence: Very low

Strength of recommendation: Conditional

Rationale:

Current evidence does not suggest any benefit in people with dementia or those with cognitive impairment, with micronutrient supplementation (vitamin B complex, vitamin E, Omega-3) or Ginkgo biloba extract or Mediterranean diet, the quality of evidence is very low and at present this should be considered inconclusive.

Remarks:

None of the primary studies available have been carried out in low- and middle-income countries. Moreover, very few randomized controlled trials to date on supplementation have been carried out in the patient groups who are deficient in the relevant micronutrient.

Vitamin E supplementation in those with dementia and adherence to a Mediterranean diet in cognitively healthy older adults may have some potential benefits on cognitive function: however, further research is required.

mhGAP Priority Condition: Alcohol use disorders

ALC1: Baclofen for relapse prevention and management among people with alcohol dependence *[New 2015]*

Recommendation

Baclofen can be offered to prevent relapse among people with alcohol dependence post-detoxification.

Quality of Evidence: Low

Strength of recommendation: Conditional

Rationale:

There is short-term evidence suggesting that baclofen improves abstinence from alcohol compared to placebo. There were no serious side effects reported; however, baclofen can cause sedation and cessation of baclofen can be associated with a mild benzodiazepine-like withdrawal syndrome. Patients value affordable and available treatments for alcohol dependence. Baclofen is available in generic form and is inexpensive. Baclofen may not available in all countries and is not registered for the use of alcohol dependence.

Remarks:

A dose of 10mg three times a day is recommended initially, but can be increased to 20mg three times a day if needed.

Baclofen should be reduced gradually rather than stopped abruptly because of the risk of a mild benzodiazepine withdrawal-like syndrome.

ALC2: Psychosocial interventions for the management of alcohol dependence *[2015]*

Recommendation ALC 2:

Psychosocial interventions including cognitive behavioural therapy (CBT), couples therapy, psychodynamic therapy, behavioural therapies, social network therapy, contingency management and motivational interventions, and twelve-step facilitation can be offered for the treatment of alcohol dependence.

Quality of Evidence: Low

Strength of recommendation: Conditional

Rationale:

Although the quality of the evidence is low, the benefits of psychosocial interventions outweigh their harms for the management of alcohol dependence. Alcohol dependence produces significant distress and decreased functioning. In terms of managing alcohol dependence people would value being able about their alcohol use and related psychological and social problems. They would also value being abstinent and reducing their drinking.

Remarks:

The list above contains those examples of structured psychosocial support that have been shown to be effective. Given the nature of psychosocial support and the limited number of countries in which the psychosocial support has been tested, it may be useful to introduce measures to routinely monitor the effectiveness of treatment, such as the retention rate and the rates of drug use in treatment, in order to know that that the treatment provided is effective.

Non-specialist health care providers require training in and supervision for delivery of psychosocial interventions.

mhGAP Priority Condition: Drug use disorders

DRU1: Psychosocial interventions for the management of cannabis dependence *[Updated 2015]*

Recommendation

Psychosocial interventions based on cognitive behavioural therapy (CBT) or motivational enhancement therapy (MET) or family therapy can be offered for the management of cannabis dependence.

Quality of Evidence: Low

Strength of recommendation: Conditional

Rationale:

Although the quality of the evidence is low, the benefits of psychosocial interventions outweigh their harms with no clinically relevant differences between individual interventions in direct comparisons. Cannabis disorders can produce significant distress and decreased functioning among some individuals. In terms of managing cannabis dependence, people would positively value being able to talk about their drug use and related psychological and social problems.

Remarks:

There may also be a role for family interventions, group interventions, and 12 step interventions.

Other forms of psychosocial support may be effective, but the evidence for this is lacking at this stage.

Non-specialist health care providers require training in and supervision for delivery of psychosocial interventions.

DRU2: Psychosocial interventions for the management of psychostimulant dependence *[2015]*

Recommendation

Psychosocial interventions including contingency management, cognitive behavioural therapy (CBT) and family therapy can be offered for the treatment of psychostimulant dependence.

Quality of Evidence: Very low

Strength of recommendation: Conditional

Rationale:

Although the quality of the evidence is very low, the benefits of psychosocial interventions outweigh their harms. Generally, there is belief that people would value being able to talk to others about their drug use and related psychological and social problems, however some value their privacy more. Non-specialist health care providers require training in and supervision for delivery of psychosocial interventions.

Remarks:
Although many of the research trials use monetary reinforcement, use of contingency management should be adapted to the culture and population with input from patients.

DRU3: Supervised dosing with a long acting opioid medication for the management of prescription opioid dependence *[New 2015]*

Recommendation
When managing people who are dependent on strong prescription opioids (i.e. morphine-like), physicians can switch to a long acting opioid (such as methadone and buprenorphine) which can be taken once daily, with supervised dispensing if necessary, either for maintenance treatment or for detoxification.

Quality of Evidence: Low

Strength of recommendation: Conditional

Rationale:

There is low quality evidence regarding the benefits of long acting opioid medication for the management of prescription opioid dependence. However both buprenorphine and methadone are medications that can be diverted from treatment to illicit sales, which is a cause for concern. Maintenance treatment might be the preferred option for patients who find it difficult to cease opioids, either because of pain recurrence or opioid dependence symptoms. In some countries, neither buprenorphine nor methadone are available and maintenance treatment is not possible due to supply chain issues. National legislation surrounding controlled drugs can also negatively impact availability.

Remarks:
The prescription of long acting opioids such as methadone and buprenorphine in the maintenance treatment of opioid dependence is most safely conducted following specific training, or under the supervision of a specialist in the treatment of opioid dependence. Within the category of "supervised long acting opioid medication", which includes methadone, buprenorphine and slow-release oral morphine, buprenorphine has most evidence of support and has a variety of advantages, including lower overdose risk and better harms profile. However, methadone can be another option, when buprenorphine is not available. If methadone and buprenorphine treatment are not available, it may be possible to substitute methadone and buprenorphine with another long acting opioid which is available and to supervise the dispensing daily if necessary.

When deciding between maintenance and detoxification options, the duration and severity of the opioid dependence, past history of illicit drug use, and patient preference should be taken into consideration.

Patients should be advised that people with opioid dependence who detox are at a higher risk of overdose having completed detoxification, as their tolerance to opioids will have dropped.

The duration of maintenance treatment is difficult to determine, but generally, the patient should not be encouraged to cease maintenance treatment until they have ceased other substance use.

For detoxification, it may be preferable to titrate the pace of reduction to the patients' capacity to manage the opioid withdrawal symptoms.

mhGAP Priority Condition: Self-harm and suicide

SUI1: School-based interventions for reducing deaths from suicide and suicide attempts among young people *[New 2015]*

Recommendation

The implementation of suicide prevention programmes in school settings that include mental health awareness training and skills training can be offered to reduce suicide attempts and suicide deaths among adolescent students.

Quality of Evidence: Low

Strength of recommendation: Conditional

Rationale:

Mental health awareness programmes that include skills training (e.g., problem solving, coping with stress) have been found to be effective in reducing suicide attempts, although the quality of the evidence is low. Potential harms may result through a lack of healthcare and community resources to provide care for at-risk adolescents who seek help.

Remarks:

Most of the described interventions have been administered and evaluated in adolescent populations of 14-17 years old.

Suicide prevention programmes, including the training of programme providers, would need to be adapted/contextualized to local religious, cultural and legal settings in a sensitive and appropriate manner.

Appendix 1: List of GDG members

LAST NAME	FIRST NAME	GENDER	COUNTRY: WHO REGION	LAMIC/ HIC	TITLE	AFFILIATION	EXPERTISE
GDG MEMBERS							
Achab	Sophia	F	Switzerland: EUR	HIC	Deputy head of the Addiction Division	Service d'addictologie, Mental Health and Psychiatry Department, University Hospital of Geneva, WHO Collaborating Centre	Psychiatry and psychotherapy: specialist in behavioural addictions
Albanese	Emiliano	M	Switzerland: EUR	HIC	Professor of public mental health	Department of Psychiatry, University of Geneva, WHO collaborating centre	Dementia, Neuro-epidemiology and Public mental health
Ali	Robert	M	Australia: WPR	HIC	Associate professor of public health and addiction medicine	Drug and Alcohol Services South Australia WHO Collaborating Centre for the Treatment of Drug and Alcohol, University of Adelaide	Substance use disorders treatment and prevention, drug and alcohol editorial board member at Cochrane
Barbui	Corrado	M	Italy: EUR	HIC	Associate professor of psychiatry	WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation, University of Verona, Italy	Global mental health, guidelines development, expertise in using GRADE, systematic review methodology
Carli	Vladimir	M	Sweden: EUR	HIC	Senior lecturer in the prevention of suicide and mental ill health	National Centre for Suicide Research and Prevention of Mental lll-Health (NASP), Karolinska Institute, Sweden	Self-harm and suicide prevention
Chatterjee	Sudipto	M	India: SEAR	LAMIC	Consultant psychiatrist	Parivartan Trust and Sangath, Bangalore, India	Severe and enduring mental disorders, development of severe mental disorders interventions in LAMICs
Cuijpers	Pim	M	Netherlands: EUR	HIC	Professor of clinical psychology	Department of Clinical Psychology, Faculty of Psychology and Education, VU University Amsterdam, Netherlands	Depression, Medically unexplained somatic complaints, meta-analysis of the efficacy of psychological interventions
Dassa	Kolou	M	Togo: AFRO	LAMIC	Psychiatrist and focal point for mental health in the Ministry of Health	Ministry of Health, Togo	Implementation of mhGAP for substance use disorders in LAMIC
Dowrick	Chris	M	United	HIC	Professor of primary medical	University of Liverpool, Institute of	Medically unexplained somatic

			Kingdom: EUR		care	Psychology, Health and Society, Liverpool, United Kingdom	complaints, mental health in primary care, guideline development (NICE) for depression
Eaton	Julian	M	Togo: AFR	LAMIC	Mental health advisor for CBM in West Africa.	CBM International, Togo, and London School of Hygiene and Tropical Medicine, United Kingdom	Global mental health, programme management, advocacy, mental health policy, community mental health care and rehabilitation in LAMIC settings
Humayun	Asma	F	Pakistan: EMR	LAMIC	Consultant psychiatrist	Meditrina Health Care, Islamabad, Pakistan	Depression, psychosocial support and interventions for mental disorders
Ivbijaro	Gabriel	M	Portugal: EUR	HIC	Medical director and chair of the World Organisation of Family Doctors working party on mental health	Wood Street Medical Centre, London, United Kingdom	Mental health in primary care
Jette	Nathalie	F	Canada: AMR	HIC	Professor of clinical neurosciences and community health sciences	Hotchkiss Brain Institute and O'Brien Institute for Public Health, University of Calgary, Alberta, Canada	Adult epilepsy, health services research, epidemiology, Chair of International League Against Epilepsy Guidelines Task Force and Guideline Process Committee
Newton	Charles	M	Kenya: AFR	LAMIC	Professor of tropical neurosciences and paediatrics	Kenya Medical Research Institute, Kilifi, Kenya	Paediatric epilepsy, epidemiology of epilepsy, neurodevelopmental disorders in LAMICs
Omigbodun	Olayinka	F	Nigeria: AFR	LAMIC	Professor of psychiatry, President of the International Association for Child and Adolescent Psychiatry and Allied Professions (IACAPAP)	Department of Psychiatry, College of Medicine, University of Ibadan & Dept. of Child & Adolescent Psychiatry, University College Hospital, Ibadan	Child and adolescent mental health, public mental health, mental health in primary care
Osei	Akwasi	M	Ghana: AFR	LAMIC	Chief psychiatrist and medical director of the Accra Psychiatric Hospital	Ghana health service (Ministry of Health), Accra, Ghana	Mental health program management, mental health law and human rights
Pemjean	Alfredo	M	Chile: AMR	LAMIC	Head of the Department of Mental Health	Secretariat for Public Health, Ministry of Health, Chile	Mental health program management
Prince	Martin	M	United Kingdom: EUR	HIC	Professor of epidemiological psychiatry and coordinator of the 10/66 dementia research group	Institute of Psychiatry, Psychology and Neuroscience, Health Service & Population Research Dept, London, United Kingdom	Dementia, global mental health, guidelines development, dementia in LAMICs
Rahman	Atif	M	Pakistan:	LAMIC	Professor of child psychiatry	University of Liverpool, Institute of	Child and adolescent mental health,

			EMR			Psychology, Health and Society, Livepool, United Kingdom	global mental health, women's mental health, psychological interventions for mental disorders in LAMICs, cultural issues in mental health care
Rawson	Richard	M	USA: AMR	HIC	Associate director of UCLA Integrated Substance Abuse Programs and professor-in-residence	Integrated Substance Abuse Programmes, UCLA Department of Psychiatry, California, United States	Substance use disorders treatment and prevention, clinical trials for treatment of substance use disorders, addiction training
Sharan	Pratap	M	India: SEAR	LAMIC	Professor of psychiatry	All India Institute of Medical Sciences, Department of Psychiatry	Adult psychiatry, public mental health, global mental health
Sharifi Senejani	Vandad	M	Iran: EMRO	LAMIC	Associate professor of psychiatry	Department of Psychiatry Tehran University of Medical Sciences, Tehran, Islamic Republic of Iran	Severe and enduring mental disorders, service implementation, clinical trials for treatment of psychosis and mood disorders
Thornicroft (Co-Chair)*	Graham	M	United Kingdom: EUR	HIC	Professor of community psychiatry	Health Service and Population Research Department, King's College London, Institute of Psychiatry Psychology and Neuroscience	Global mental health, guidelines development, mental health services research, mental health stigma.
Vijayakumar	Lakshmi	F	India: SEAR	LAMIC	Associate professor of psychiatry	Voluntary Health Services Chennai, Department of Psychiatry and SNEHA, Suicide Prevention Centre, Chennai, India	Suicide prevention, global suicide research
Weissbecker	Inka	F	USA: AMR	HIC	Global mental health and psychosocial advisor	International Medical Corps, Washington, United States	Depression, medically unexplained somatic complaints, public mental health, mental health interventions in low resource settings, mental health in emergency situations
Zhao	Min	F	China: WPR	LAMIC	Professor of psychiatry and vice president of the Shanghai Drug Abuse Treatment Centre	Shanghai Drug Abuse Treatment Centre, Shanghai Mental Health Centre, Shanghai Jiaotong University School of Medicine	Substance use disorders treatment and prevention, mental health and addiction

**** Shekhar Saxena (co-chair), Director, Department of Mental Health and Substance Abuse, WHO, Geneva, Switzerland***

LAMIC: Low- and Middle-income country/HIC: High-income country

Appendix 2: Note for the Record

mhGAP Guideline Development Group Meeting

3-5 December 2014

Declaration of Interest Review

Responsible Officer – Tarun Dua

The declaration of interest forms submitted by the mhGAP Guideline Development Group (GDG) was reviewed. An interest has been declared by the experts mentioned below and their significance and assessment is indicated after consultation with the Director of the Department.

1. Robert Ali – The declared interest was assessed to be significant but relates only to one areas of the GDG's work – (i.e., opioid substitution treatment). It was proposed that the said experts is excluded from the decision making process related to the guideline key question relevant to the area of opioid substitution (partial exclusion). Please note that the said expert did not participate in the GDG meeting 3-5 December 2014. After consultation with the Chair of GDG, the reported interest was publically disclosed to other meeting participants and was recorded and will be disclosed in the report of the meeting and/or relevant publications.
2. Vladimir Carli - It was assessed that the declared interest was insignificant or minimal as it was only tangentially related to the subject of the work under consideration.
3. Sudipto Chatterjee – It was assessed that the declared interest was insignificant or minimal as it was only tangentially related to the subject of the work under consideration.
4. Julian Eaton - It was assessed that the declared interest was insignificant or minimal as it was only tangentially related to the subject of the work under consideration.
5. Atif Rahman – It was assessed that the declared interest was insignificant or minimal as it was only tangentially related to the subject of the work under consideration.
6. Richard Rawson – The declared interest was assessed to be potentially significant, as the nature of the interest is mostly research funding from federal agencies (with some amount from philanthropic foundation). We proposed conditional participation of the said expert. After consultation with the Chair of GDG, the reported interest was publically disclosed to other meeting participants and was recorded and disclosed in the report of the meeting and/or relevant publications.
7. Pratap Sharan – The declared interest was assessed to be not relevant to the area under consideration.
8. Graham Thornicroft - It was assessed that the declared interest was insignificant or minimal as it was only tangentially related to the subject of the work under consideration.

Appendix 3: Overview of declarations of interest from GDG members

Name	GDG member in 2009	DOI information	Type of declaration	Management decision
Sophia Achab	No	Nothing declared	N/A	N/A
Emiliano Albanese	No	Nothing declared	N/A	N/A
Robert Ali	No	Answered "yes" to question 2a. *The university of Adeleide received a united educational grant from Reckitt Benckiser to conduct research in 2014 (240, 000 [no currency]). The company is a manufacturer of health cleaning products, medicines, including buprenorphine, and household goods.*	Academic/Financial	Conflict of interest (CoI) was assessed to be significant but relates only to one areas of the GDG's work – i.e. opioid substitution treatment – *refer to the Note for the Record for details.*
Corrado Barbui	Yes	Nothing declared	N/A	N/A
Vladimir Carli	No	Answered "yes" to questions 1a and 2a. *Dr Carli works for the National Centre for Suicide Research and Prevention in Sweden. His daily work is as a researcher in the field. His unit regularly applies for grants at national and international (EU and NIH) and levels for grants related to research projects in the field of suicide prevention.*	Public	CoI is insignificant or minimal and requires no action beyond declaration at the meeting and reporting in the final guideline.
Sudipto Chatterjee	No	Answered "yes" to question 2a. *Dr Chatterjee was the Trial Coordinator of a Wellcome Trust funded RCT- Community care for people in India (COPSI) in 2013, GBP 3,000.*	Academic	CoI is insignificant or minimal and requires no action beyond declaration at the meeting and reporting in the final guideline.
Wilhelmus Cuijpers	No	Nothing declared	N/A	N/A
Chris Dowrick	No	Answered "yes" to question 5b. *Board Advisor to Mersey Care NHS Trust since December 2010. Mersey Care is a statutory NHS organization providing a wide range of mental health services in northwest England.*	Public	CoI requires no action beyond declaration at the meeting and reporting in the final guideline.
Kolou Simliwa	No	Nothing declared	N/A	N/A

Dassa				
Julian Eaton	No	Answered "yes" to questions 1a, 1b, 2a, 5a and 5b. *Dr Eaton is employed as mental health advisor for CBM International and his daily routine includes supporting service development and producing normative materials and guidelines (1a and b). CBM has funded research in service evaluation (2a). Dr Eaton regularly speaks and writes on mental health, including for WHO and at WHO events.*	Public	CoI is insignificant or minimal and requires no action beyond declaration at the meeting and reporting in the final guideline.
Asma Humayun	No	Nothing declared	N/A	N/A
Gabriel Ivbijaro	No	Nothing declared	N/A	N/A
Nathalie Jette	No	Nothing declared	N/A	N/A
Charles Newton	No	Nothing declared	N/A	N/A
Olayinka Omigbodun	Yes	Nothing declared	N/A	N/A
Akwasi Osei	No	Nothing declared	N/A	N/A
Alfredo Pemjean	No	Nothing declared	N/A	N/A
Martin Prince	Yes	Nothing declared	N/A	N/A
Atif Rahman	Yes	Answered "yes" to questions 1a, 1b, 2a and 2b. *He holds an academic position conducting and supervising research in the field of mental health (1a). He is an honorary of a non-profit NHS trust in the United Kingdom (1b). As a full time academic, he regularly receives research grants (GBP 2million over 5 years) for mental health research from Wellcome trust, NIH, Grand Challenges, British council, Alder-Hey NHS Trust (2a). Prof Rahman is also a consultant for a Human Development Research Foundation project in Pakistan (2b).*	Academic/ Public	CoI is insignificant or minimal and requires no action beyond declaration at the meeting and reporting in the final guideline.
Richard Rawson	No	Answered "yes" to questions 1b and 2a. *Richard used to give consultancies to the National Rehabilitation Centre of Abu Dhabi for UDS 20,000 for three years (1a). He currently receives a research grant (USD 5,000,000) from the US National Institute on Drug Abuse for training and screening and brief intervention research project. Richard also receives evaluation grants from the US government (USD 250,000 per year) and department of state (USD*	Academic/ public	CoI is potentially significant but requires no action beyond declaration at the meeting and reporting in the final guideline.

		400,000 for two years) as well as from Drosos Foundation, a charitable non-profit organization, which aims to improve the living conditions of disadvantaged people http://www.drosos.org/en (USD 125,000).		
Pratap Sharan	No	Answered "yes" to question 2a. *Dr Sharan has received USD 20,000 between 2011 - 2013 to support clinical trials for the effectiveness of Duloxetine for fibromyalgia.*	Academic	CoI not relevant to area and requires no action beyond declaration at the meeting and reporting in the final guideline.
Vandad Sharifi	No	Nothing declared	N/A	N/A
Graham Thornicroft	Yes	Answered "yes" to questions 1a and 2a. *Prof Thornicroft is employed as professor of community psychiatry at Kings College London. He is also chair of the Global Initiative in Psychiatry and the Maudsley International Institute of Psychiatry. He doesn't see that any of these declarations should have an effect on his role as chair.*	Academic	CoI is insignificant or minimal and requires no action beyond declaration at the meeting and reporting in the final guideline.
Lakshmi Vijayakumar	Yes	Nothing declared	N/A	N/A
Inka Weissbecker	No	Answered "yes" to questions 1a and 6c. *Employed by International Medical Corps, which has an interest in the subject of mental health and distress related to humanitarian crises (as IMC has various global projects integrating mental health and psychosocial support) (1a). IMC has paid for some travel costs before related to WHO meetings (6c).*	Public	CoI requires no action beyond declaration at the meeting and reporting in the final guideline.
Min Zhao	No	Nothing declared	N/A	N/A

Appendix 4: Details related to the search strategy and summation of evidence and electronic databases routinely searched for each key question

In consultation with GDG members and in collaboration with technical experts, the WHO secretariat developed the method for the evidence review process for updating the recommendations. The scope of work included reviewing and commenting on the draft PICO questions, conducting comprehensive literature searches and evidence syntheses and providing reports, including GRADE tables.

Specifically, technical experts identified for the evidence review process undertook the following tasks:

a. **Finalization PICO (Population, Intervention, Comparison, Outcome) questions for the systematic review.** Technical experts reviewed and commented on the draft PICO questions before they were finalized to ensure that the questions are answerable with the proposed scope of the systematic review.

b. **Development of search strategies, searching of relevant bibliographic databases and identification of systematic reviews that fulfil the PICO terms.** Technical experts, in consultation with WHO librarians or other experts in information retrieval, conducted comprehensive searches of major bibliographic databases (listed below) in order to identify one or more systematic review(s) that matched the PICO terms. Only high-quality, recent systematic reviews were used to draft evidence profiles. If only low-quality or not recent systematic reviews were identified, new systematic reviews were commissioned.

c. **Preparation of GRADE Evidence Profiles.** Technical experts assessed the quality of the evidence using GRADE and produced evidence profiles for each critical and important outcome.

Bibliographic databases that were searched:

- Cochrane Library
- BMJ Clinical Evidence
- NICE Guidelines
- PubMed/MEDLINE
- EMBASE
- PSYCINFO.

Databases relevant for LMIC:

- WHO regional database: http://www.who.int/library/databases/en/
- Global Health Library: http://www.globalhealthlibrary.net/php/index.php
- WHOLIS: http://dosei.who.int/uhtbin/webcat
- Database of Impact Evaluations: http://www.3ieimpact.org/database_of_impact_evaluations.html
- PAHO Library Catalogue: http://bases.bireme.br/cgi-bin/wxislind.exe/iah/online/?IsisScript=iah/iah.xis&base=PAHO&lang=i

- African Index Medicus (AIM): http://indexmedicus.afro.who.int/cgi-bin/wxis.exe/iah/?IsisScript=iah/iah.xis&lang=I&base=AIM
- AFROLIB Database: http://afrolib.afro.who.int/cgi-bin/wxis.exe/iah/?IsisScript=iah/iah.xic&lang=I&base=afrolib
- ArabPsycNet: http://www.arabpsynet.com/paper/
- EurasiaHealth: http://www.eurasiahealth.org/
- HERDIN NeON Database: www.herdin.ph
- Hrcak: http://hrcak.srce.hr/index.php
- IndMED: http://indmed.nic.in/
- IranMedex: http://www.iranmedex.com/english/index.asp
- KoreaMed: http://www.koreamed.org/SearchBasic.php
- LILACS: http://bases.bireme.br/cgi-bin/wxislind.exe/iah/online/?IsisScript=iah/iah.xis&base=LILACS&lang=i
- Africal Journals OnLine (AJOL): http://www.ajol.info/

Scientific journals with a specific interest for LAMICs that were hand-searched:

- BMC International Health and Human Rights
- Bulletin of the World Health Organization
- Health Policy and Planning
- International Journal of Mental Health Systems
- Lancet Global Health
- PLoS Medicine

Search outputs grouped into
(1) Guidelines;
(2) Systematic reviews; and
(3) Individual studies
which were searched if systematic reviews were not available and/or depending on the PICO question.

Appendix 5: Guiding principles for technical experts to assess the quality of evidence included in evidence profiles

GENERAL PRINCIPLES

In order to assess the quality of evidence using the GRADE template, it is essential that raters agree on basic criteria to be used to downgrade or upgrade the evidence. This is required to enhance the consistency and reliability of ratings.

General principles:

(1) A first rater grades the quality of evidence for each outcome, and summarizes findings using the GRADE template for each outcome. Ratings are required to be checked for consistency by a second member of the review group. Agreement between raters is reached (a third rater is involved in case of disagreement).

(2) When assessing the quality of evidence, the GRADE general approach is followed:

- GRADE is not a quantitative system for grading the quality of evidence. Each factor for downgrading or upgrading does not reflect discrete categories. Instead, each factor reflects **a continuum within each category and among the categories**. When the body of evidence is intermediate with respect to a particular factor, the decision about whether a study falls above or below the threshold for up- or downgrading the quality (by one or more factors) depends on judgment.

- Despite the limitations of breaking continua into categories, treating each criterion for rating quality up or down as discrete categories enhances transparency. Indeed, **the great merit of GRADE is not that it ensures reproducible judgments but that it requires explicit judgment that is made transparent to users.**

NOTE: Observational studies that have been downgraded to very low quality for any reason should not be upgraded.

(3) To achieve transparency and implicity, the GRADE system classifies the quality of evidence in one of four grades:

Grade	Definition
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the

	estimate.
Very low	Any estimate of effect is very uncertain.

(4) According to the GRADE system, raters are required to make a judgement on studies included in systematic reviews with respect to the following criteria:

A. LIMITATIONS (RISK OF BIAS)
B. INCONSISTENCY
C. INDIRECTNESS
D. IMPRECISION

(5) REPORTING BIAS

(A) LIMITATIONS (risk of bias)

Definition: Limitations in the study design and implementation may bias the estimates of the treatment effect.

Our confidence in the estimate of the effect and in the following recommendation decreases if studies suffer from major limitations. The more serious limitations are, the more likely it is that the quality of evidence is downgraded. Our confidence in an estimate of effect decreases if studies suffer from major limitations that are likely to result in a biased assessment of the intervention effect. For randomized trials, the following limitations are likely to result in biased results: lack of allocation concealment, lack of blinding, incomplete accounting of patients and outcome events, selective outcome reporting, other (for further details see the GRADEprofiler instructions).

The following criteria are followed by WHO raters on LIMITATIONS:

If one or more of the three criteria reported below is not met in up to 10% of trials included in the systematic review = no downgrading (negligible limitations)

If one or more of the three criteria reported below is not met in 10-30% of trials included in the systematic review = - 1 (serious limitations)

If one or more of the three criteria reported below is not met in more than 30% of trials included in the systematic review = - 2 (very serious limitations)

The three criteria are:

(1) trials are described as randomised;

(2) outcome assessment is described as masked;

(3) dropout rate (both treatment arms) is below or equal to 30% (and dropouts are similarly distributed between treatment arms).

(B) INCONSISTENCY

Definition: Inconsistency refers to an unexplained heterogeneity of results across studies.

Widely differing estimates of the treatment effect (i.e. heterogeneity or variability in results) across studies suggest true differences in underlying treatment effect. When heterogeneity exists, but investigators fail to identify a plausible explanation, the quality of evidence is downgraded by one or two levels, depending on the magnitude of the inconsistency in the results (for further details see the GRADEprofiler instructions). Inconsistency may arise from differences in:

- populations (e.g., medications may have larger relative effects in sicker populations)
- interventions (e.g., larger effects with higher medication doses)
- outcomes (e.g., diminishing treatment effect with time).

Guideline panels or authors of systematic reviews also consider the extent to which they are uncertain about the underlying effect due to the inconsistency in results and they may downgrade the quality rating by one or even two levels.

The following criteria are followed by WHO raters on INCONSISTENCY:

If visual investigation of forest plots suggests some degree of heterogeneity (supported by a formal test of heterogeneity indicating some degree of heterogeneity, for example I-squared between 50% and 75%) = - 1 (serious inconsistency)

If visual investigation of forest plots suggests high degree of heterogeneity (supported by a formal test of heterogeneity indicating high heterogeneity, for example I-squared higher than 75%) = - 2 (very serious inconsistency)

NOTE: Raters don't downgrade for inconsistency when only one study contributes to the evidence base.

(C) INDIRECTNESS

Definition: There are two types of indirectness:

1. Indirect comparison – occurs when a comparisons of intervention A versus B is not available, but A was compared with C and B was compared with C. Such studies allow indirect comparisons of the magnitude of effect of A versus B. Such evidence is of lower quality than head-to-head comparisons of A and B would provide.

2. Indirect population, intervention, comparator, or outcome – The question being addressed by the guideline panel or by the authors of a systematic review is different from the available evidence regarding the population, intervention, comparator, or an outcome.

Indirectness may additionally refer to the extent to which the characteristics of those who will deliver the intervention in the real-world (including context characteristics) match with the characteristics of those who actually delivered the intervention under experimental conditions (in terms of background education, training, referral possibilities, context, other features).

Those making recommendations or authors of systematic reviews consider the extent to which they are uncertain about the applicability of the evidence to their relevant question and downgrade the quality rating by one or even two levels.

The following criteria are followed by WHO raters on INDIRECTNESS: The question being addressed by the guideline panel is different from the available evidence regarding the population, intervention, comparator, outcome or regarding the characteristics of those who will deliver the intervention = - 1 (serious doubts about directness) The question being addressed by the guideline panel is markedly different from the available evidence regarding the population, intervention, comparator, outcome or regarding the characteristics of those who will deliver the intervention = - 2 (very serious doubts about directness)

NOTE: If only one study contributes to the evidence base, raters may consider if this affects directness and, if yes, downgrading may be appropriate.

(D) IMPRECISION

Definition: Results are imprecise when studies include relatively few patients and few events and, therefore, have wide confidence intervals around the estimate of the effect.

In this case guideline panel judges the quality of the evidence lower than it otherwise would have been because of the uncertainty in the results (for further details see the GRADEprofiler instructions).

The following criteria are followed by WHO raters on IMPRECISION:
 	
If (a) the overall number of individuals included in trials is low (between 200 and 100 individuals, both treatment arms) or (b) the 95% confidence interval includes both 1) no effect and 2) appreciable benefit or appreciable harm = - 1 (serious imprecision)
 	
If (a) the overall number of individuals included in trials is very low (less than 100 individuals, both treatment arms) and (b) the 95% confidence interval includes both 1) no effect and 2) appreciable benefit or appreciable harm = - 2 (very serious imprecision)
 	
NOTE: For continuous outcomes "no effect" means a standardized mean difference (SMD) with a confidence interval that crosses zero; appreciable benefit or appreciable harm means that the upper or lower confidence limit crosses an effect size of 0.5 in either direction. For dichotomous outcomes "no effect" means an estimate with a confidence interval that crosses one; appreciable benefit or appreciable harm means that the upper or lower confidence limit crosses a risk of 2.0 or 0.5.

(E) REPORTING BIAS

Definition: Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies. Publication bias arises when investigators fail to report studies they have undertaken (typically those that show no effect).

Methods to detect the possibility of publication bias in systematic reviews exist, although authors of the reviews and guideline panels must often guess about the likelihood of publication bias. A prototypical situation that should elicit suspicion of publication bias occurs when published evidence is limited to a small number of trials, all of which are showing benefits of the studied intervention.

The following criteria will be followed by WHO raters on REPORTING BIAS: If the graphical inspection of the funnel plot suggests some asymmetry, or if any other reasons (to be recorded as footnote) suggest that reporting bias might have had an impact on the overall summary estimate (for example: unpublished grey literature was not included) = - 1 If the graphical inspection of the funnel plot suggests high asymmetry, or if any other reasons (to be recorded as footnote) suggest that reporting bias might have had a high impact on the overall summary estimate (for example: unpublished grey literature was not included) = - 2 *A different criterion may be followed by WHO raters in exceptional situations. Explanation should be reported as footnote in the corresponding GRADE table.*

Upgrading the evidence

Please note that the randomized trials downgraded for any reason, can't be upgraded.

(6) DOSE-RESPONSE GRADIENT

PLEASE NOTE: The dose-response gradient is assessed only in observational studies not downgraded for any reason.

The presence of a dose-response gradient may increase our confidence in the findings of observational studies and thereby increase the quality of evidence. Only observational studies with no threats to validity (not downgraded for any reason) can be upgraded.

(7) LARGE MAGNITUDE OF EFFECT

You should assess if the effect was large or very large and, if so, upgrade the quality of evidence accordingly for this outcome. For observational studies, only studies with no important threats to validity (not downgraded for any reasons) can be upgraded.

To rate magnitude of the effect:

- If the effect was not large (RR between 0.5 and 2.0) choose no

- If the effect was large (RR either >2.0 or <0.5 based on consistent evidence from at least 2 studies, with no plausible confounders) choose RR >2 or <0.5
  «this will upgrade the quality of evidence for this outcome by 1 level»
- If the effect was very large (RR either >5.0 or <0.2 based on direct evidence with no major threats to validity) choose RR >5 or <0.2
  «this will upgrade the quality of evidence for this outcome by 2 levels»
- Explain your choice in a footnote whenever you upgrade the quality of evidence for any reason, because it is important for others to understand the rationale for your choice.

(8) EFFECT OF ALL PLAUSIBLE CONFOUNDING

On occasion, all plausible confounding may be working to reduce the demonstrated effect or increase the effect if no effect was observed.
For example, if only sicker patients receive an experimental intervention or exposure, yet they still fare better, it is likely that the actual intervention or exposure effect is larger than the data suggest. For observational studies, only studies with no important threats to validity (not downgraded for any reasons) can be upgraded.