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Update of the World Health Organization's Mental Health Gap Action Programme Guideline for Psychoses (Including Schizophrenia)

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***Background and Hypothesis*: The World Health Organization's (WHOs) Mental Health Gap Action Programme (mhGAP) aims to improve healthcare for mental, neurological, and substance use disorders in nonspecialized settings, with a focus on low- and middle-income countries (LMICs). mhGAP includes guidelines for the treatment of psychoses (including schizophrenia), which were recently updated in 2023. The complexity of the WHO guideline update process and the updated recommendations on psychoses are presented. *Study Design*: The WHO guideline development process is outlined as well as the evidence appraisal and the translation of the evidence into recommendations following the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology. The guideline update process includes a review of the literature, a compilation of systematic reviews, and extracting data related to critical and important outcomes. The updated recommendations and the justifying evidence are discussed. *Study Results*: The WHO mhGAP guidelines for psychoses are adapted to LMICs, and consist of 13 recommendations in 2023, whereof 5 were updated, and 1 recommendation was newly developed. Background information on how these recommendations were obtained, and significant changes since the previous guideline update in 2015 are provided. *Conclusions*: Unlike other guidelines, the WHO must consider various countries, contextual factors, and the WHO Model Lists of Essential Medicines when developing its guidelines. A transformation of the WHO guideline for psychoses into a living guideline would ensure always up-to-date recommendations and facilitate shared decision-making.**

Key words: schizophrenia/evidence-based guidelines/living guideline/antipsychotics/guideline recommendation

Background

Schizophrenia affects approximately 24 million people worldwide.[1] Most individuals living with schizophrenia across the world, particularly in low- and middle-income countries (LMICs), do not receive adequate healthcare and lack access to essential treatment options.[1] The resources allocated for the treatment of mental, neurological, and substance (MNS) use disorders are insufficient and inequitably distributed, leading to a treatment gap exceeding 75%.[2,3] Compared with high-income countries, people with MNS disorders receive 3 times less treatment in LMICs.[4] The World Health Organization's (WHOs) Mental Health Gap Action Programme (mhGAP), launched in 2008 and uptaken in over 100 countries, was developed with considerations of treatment options in LMICs in mind, that have large proportions of the global burden of MNS disorders.[5,6] The mhGAP provides health planners, policymakers, and donors with a comprehensive collection of activities and programs, while also considering potential constraints to improving care.[2] The program aims to enhance the dedication of stakeholders to increase the allocation of financial and human resources for the care of MNS disorders, and to expand coverage of evidence-based key interventions for the prevention and treatment of priority conditions, even when resources are scarce and only nonspecialist healthcare available.[2,7] Priority conditions include MNS use disorders with a high burden in terms of mortality, morbidity, and disability, as well as large economic costs or association with human rights violations.[2] These conditions comprise depression, psychoses, self-harm/suicide, epilepsy, dementia, substance use disorders, and mental disorders in children and adolescents.[2] The development of evidence-based guidelines for MNS use disorders is

an essential component of the mhGAP.[8] The mhGAP guideline for the treatment of psychoses (including schizophrenia) and bipolar disorder was last updated in 2015.[9] Since then, a significant amount of new evidence has emerged requiring thorough reassessment. As guidelines should provide up-to-date treatment options based on the best available evidence,[10,11] an update was essential to guarantee adequate patient care.[11] The guideline for psychoses includes 13 recommendations, whereof 5 recommendations required an update and 1 recommendation was newly developed. The aim of this article is to present the WHOs guideline development process, the 2023 updated recommendations, and how they were formulated as well as significant changes since the previous guideline update in 2015. Finally, the particularities of the WHO guideline compared with other national guidelines and the possibility of transforming the WHO guideline on psychoses into a living guideline are discussed.

Methods

We present an overview of the general guideline development process, and the development of the recommendations following the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) guideline development methodology. This is followed by a discussion of the updated recommendations and the evidence taken into consideration during formulation.

Overview of the Guideline Development Process

The guideline development process followed the methods outlined in the World Health Organization's (WHOs) Handbook for Guideline Development, which is mainly based on the GRADE methodology.[12,13] Five working groups are involved in the guideline development process, (1) the *steering group*, including members from all WHO departments and regional offices, which oversees the guideline development process, (2) the *Guideline Development Group* (GDG), represented by external multidisciplinary experts, who formulate the recommendations, (3) the *Topic Expert Groups*, experts for single modules of the guideline, (4) the *external review group*, that participates in different stages of the guideline development, and (5) the *systematic review team*, which provides a comprehensive synthesis of the evidence to inform each recommendation.[12,14] During the guideline update process, evidence profiles were developed by the systematic review team summarizing the respective evidence with a quality assessment following the GRADE methodology. The evidence profiles were prepared in close cooperation with the steering group and the external review group and were presented to the GDG during a meeting in Geneva, Switzerland, in September and December 2022. For making a decision, the GDG discusses the evidence profiles in detail by taking into account (1) the quality of the evidence on benefits and harms, (2) the values, preferences, and feasibility of the proposed intervention, and (3) the availability of resources in LMICs.[11] The GDG aims to reach a unanimous agreement on each of the mhGAP update recommendations.[11,14] Figure 1 presents a more detailed overview of the guideline development process, and figure 2 outlines the main features of the mhGAP. The authors of the article C.L., I.B., and S.L. were part of the systematic review team responsible for the development of the evidence profiles, while AA and HF were part of the WHO internal Secretariat Team (belongs to the steering group) responsible for the update of the psychoses module of the guidelines.

Update of Key Questions

Key questions, more precisely defined by PICO questions (an acronym for participants, intervention, comparator, outcome), form the basis and the starting point in the development of the guideline recommendations. For the guideline update process, the WHO takes into account (1) the emergence of new evidence from 2014 onwards, (2) suggestions and proposals for future updates from WHO implementation programs in LMICs, that are based on WHO guideline recommendations, and (3) feedback from experts and healthcare providers familiar with using WHO guideline recommendations.[11] The Steering Group (with support from the Topic Expert Group) monitors when an update of the key questions is required and drafts the key questions in PICO format, whereas the GDG finalizes the key questions.[12] Overall, the 2023 mhGAP guidelines include 48 updated recommendations for the treatment of MNS use disorders, besides 90 preexisting guideline recommendations, that required no update.[14] Until the update in 2023, the WHO guideline for psychoses consisted of 12 key questions/recommendations. These key questions and recommendations from 2015 were reviewed for the update process by the Topic Expert Groups: 5 recommendations required an update, and 1 recommendation was newly developed, thus the updated WHO guidelines for psychoses consist of 13 recommendations. The Topic Expert Groups are asked to decide whether the existing recommendations should be removed, validated, edited, or updated.[14] For an overview of the updated and preexisting key questions, please see appendix table 1.

The key questions can be classified into 4 categories[11]:

- New significant evidence emerged: an update of the recommendations is needed (PSY1, PSY2, and PSY4).
- The PICO question changed: an update is needed (PSY5 and PSY10).
- A new key question and PICO are required: a new recommendation is drafted (PSY11).
- There is no significant new evidence and the PICO remains unchanged: no need for an update process (the preexisting 7 WHO psychoses recommendations).

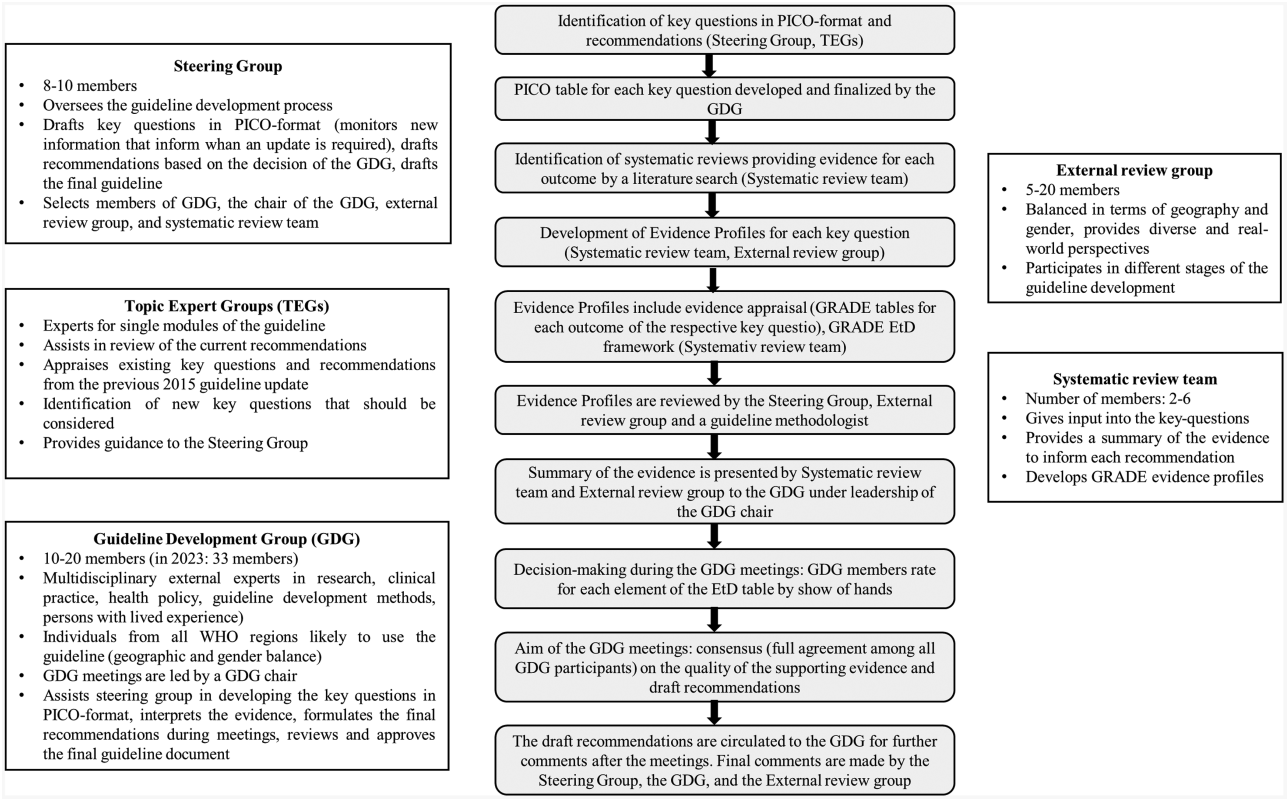

Fig. 1. Overview of the Guideline Development Process and the groups involved in the development of the guideline. *Note*: EtD framework, Evidence-to-Decision framework; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation methods. *Source*: Refs. [12,14].

Mental Health Gap Action Programme (mhGAP)

- Aims to reduce the treatment gap for mental, neurological and substance use (MNS) disorders
- Provides a collection of activities and programmes to health planners, policy makers, and donors
- Wants to increase the allocation of financial and human resources for the care of MNS disorders
- Aims to expand coverage of evidence-based key interventions for the prevention and treatment of priority conditions
- Focus on low-and middle-income countries, and non-specialized health-care
- Development of evidence-based guidelines as an essential component
- Includes the following priority conditions: Alcohol use disodrders (ALC), Anxiety (ANX) Child and adolescent mental disorders (CAMH), Conditions related to stress (STR), Dementia (DEM), Depression (DEP), Drug use disorders (DRU), Epilepsy and seizures (EPI), Overarching areas (OVE), Psychosis and bipolar disorder (PSY), Self-harm and suicide (SUI)
- Priority conditions: mental, neurological and substance use (MNS) disorders with a high burden in terms of mortality, morbidity and disability, large economic costs, association with human rights violations

Fig. 2. Overview of the main features of the Mental Health Gap Action Programme (mhGAP).[14]

Literature Search

The search was conducted externally by a professional information specialist, the Nottinghamshire Healthcare Foundation Trust (see Acknowledgments). A comprehensive search of major bibliographic databases was performed in the following databases: The Cochrane Database of Systematic Reviews, PubMed, EMBASE, PsycINFO, and Global Index Medicus. The search strategy was aligned with the PICO terms, and systematic reviews of randomized controlled trials published from 2014 onwards were targetted: Pharmacological and psychological/psychosocial interventions were compared with any other interventions, placebo, or waiting list in people with psychotic disorders (including first episode psychosis, schizophrenia, and bipolar disorder). The flow chart for each updated PICO question can be found in appendix figures 1–6.

Grading of the Evidence

The quality of the evidence of the studies was evaluated following the GRADE methodology.[13] The quality assessment includes study design, and grading of risk of bias, inconsistency, indirectness, imprecision, and publication bias.[13] The quality of evidence is graded for each patient-important outcome, and afterward, the overall quality of evidence is assessed across outcomes (ie, the body of evidence).[13] The GDG and the Steering Group select critical and important patient outcomes that will guide the evidence.[12] According to GRADE for guideline panels, the quality of evidence indicates the level of confidence we have in an estimate of the effect and its ability to support a specific recommendation.[13] The quality of a body of evidence is classified into 1 of 4 grades[13]:

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

From Evidence to Recommendations

During the GDG meetings, under the leadership of the GDG chair, the evidence profiles including the GRADE Evidence-to-Decision (EtD) frameworks are presented to the GDG by the systematic review team and the external review group. The GDG is composed of individuals from all WHO regions, external experts in research, clinical practice, health policy, guideline development methods, and persons with lived experience and balanced in gender and geographically.[14] The GDG rates for each element of the EtD framework by hand signs and aims to reach unanimous consent on the quality of the supporting evidence and draft recommendations.[14] The GRADE EtD framework includes various domains, ie, the priority of the problem, desirable anticipated effects, undesirable anticipated effects, certainty of the evidence of effects, balance between desirable and undesirable effects, values and preferences of intended users, resource requirements, certainty of the evidence of resource requirements, cost-effectiveness, impact on health equity, equality and nondiscrimination, and implementation feasibility.[14] WHO has adapted the original GRADE methods for the EtD framework and added WHO-specific criteria, ie, alignment with human rights principles and sociocultural acceptability. Due to the WHO Constitution, WHOs recommendations and guidelines must integrate equity, human rights, gender, and the social determinants of health.[12] The alignment with human rights demands each intervention to comply with international human rights and other considerations outlined in international human rights law, beyond the right to health.[12] The second WHO-specific criterion, sociocultural acceptability, is time- and context-specific, and takes into account if relevant stakeholders and those implementing an intervention consider it appropriate.[12]

The GRADE EtD framework aims to help guideline panels move from evidence to recommendations, and facilitate the decision-making process.[13] Considering all these aspects, the GDG results in a recommendation, which can be strong or conditional according to GRADE. The strength of a recommendation expresses the degree to which the GDG is confident in the balance between desirable effects and undesirable effects of an intervention.[12,13] The GDG makes a strong recommendation when being very certain about this balance and the desirable consequences clearly outweigh the undesirable consequences.[12] The GDG issues a conditional recommendation, however, when it is uncertain about this balance regarding desirable and undesirable consequences.[12] Appendix table 2 provides an overview of interpreting the strength of a recommendation and the implications for patients, clinicians, and policymakers. The draft recommendations are ultimately finalized by the Steering Group, the GDG, and the external review group.

Results

The 2023 WHO recommendations on psychoses are summarized in table 1. The nonupdated WHO recommendations are included in supplementary table S1. These were reviewed for topicality and remain valid in their current form.[14]

Table 1. The 2023 Updated WHO Recommendations on Psychoses (Including Schizophrenia)

Key question PSY1: In adults with psychotic disorders (including schizophrenia) is antipsychotic medication safe and effective?		
Updated Recommendation 2023 (PSY1)		
Recommendation(s)	Strength of Recommendation	Certainty of Evidence
1.1 Oral antipsychotic medicines—namely aripiprazole, chlorpromazine, haloperidol, olanzapine, paliperidone, quetiapine, risperidone—should be offered for adults with a psychotic disorder (including schizophrenia), carefully balancing effectiveness, side-effects, and individual preference.	**Strong**	**Moderate**
1.2 Clozapine should be considered for adults with treatment-resistant psychotic disorder (including schizophrenia) under mental health specialist supervision, carefully balancing effectiveness, side-effects, and individual preference.	**Conditional**	**Moderate**
Justification • After performing a literature search, evidence was extracted from 3 systematic reviews: Ceraso et al (75 RCTs on antipsychotic medicines in schizophrenia),[15] Leucht et al (167 RCTs on antipsychotic medicines in schizophrenia),[16] and Schneider-Thoma et al (596 RCTs on serious adverse events and mortality of second-generation antipsychotic medicines).[17] • Antipsychotics showed moderate effect sizes for overall efficacy, while differences in efficacy between medications were either small or uncertain.[16] • Antipsychotics were associated with various side-effects, the propensity differed between the agents, and the differences were overall more distinct than the efficacy differences.[16] Remarks • The medicines included in the recommendation correspond to the WHO EML[18] and are listed in alphabetical order. • Clozapine should be offered for treatment-resistant psychosis and should only be offered where lab tests are available to monitor white blood cell count, and under a mental health specialist supervision. • Medicines should be offered in combination with psychotherapy (see PSY10). Implementation considerations • People living with psychotic disorders should be involved in medicine choice in a supported decision-making process, without coercion and in line with human rights instruments. • Disruption in medicine supply (common in low- and middle-income countries) may interfere with continuation of treatment. • For the treatment of psychotic disorders, the WHO EML[18] includes the following oral medicines: - haloperidol (therapeutic alternative chlorpromazine) - risperidone (therapeutic alternatives: aripiprazole, olanzapine, paliperidone, quetiapine) - complementary list: clozapine. Research gaps • Data on first-generation antipsychotics with few exceptions such as haloperidol and chlorpromazine were very limited. As these medicines are of lower cost, further trials on some of them with relevant pharmacological properties would be warranted.		
Previous Recommendation 2012		
Recommendation(s)	Strength of Recommendation	Certainty of Evidence
Haloperidol or chlorpromazine should be routinely offered to individuals with psychotic disorder (including schizophrenia).	Strong	Very low
Second-generation antipsychotics (with exception of clozapine) may be considered in individuals with psychotic disorders (including schizophrenia) as an alternative to haloperidol or chlorpromazine if availability can be assured and cost is not a constraint.	Conditional	Low
For individuals with psychotic disorders (including schizophrenia) who do not respond to adequate dose and duration of other antipsychotic medicines, clozapine may be considered by nonspecialist healthcare providers, preferably under the supervision of mental health professionals, only if routine laboratory monitoring is available.	Conditional	Low
In individuals with psychotic disorders (including schizophrenia), minimal effective dose of antipsychotics should be used, paying attention to minimizing adverse effects.	Strong	Very low
In women with psychotic disorders (including schizophrenia) who are planning a pregnancy or pregnant or breastfeeding, low-dose oral haloperidol or chlorpromazine may be considered.	Conditional	Low
Note: Strength of recommendation: strong or conditional according to GRADE; quality of evidence: very low, low, moderate, or high. Underlying evidence 2023[15–17]; underlying evidence 2012.[19–21] Source updated recommendation and comments,[14] source recommendations from 2012.[22] The justification, remarks, implementation considerations, and research gaps were developed in cooperation between the Guideline Development Group, the External review group, and the systematic review team. The updated recommendations are highlighted in bold and only these are discussed in the main text. The previous versions of updated recommendations are also shown (shaded in gray), to see how the recommendations have changed during the update process.		

Table 1. Continued

Key question PSY2: In adults with a first psychotic episode (schizophrenia) with full remission, how long should antipsychotic medication be continued after remission in order to allow for the best outcomes?		
Updated Recommendation 2023 (PSY2)		
Recommendation(s)	Strength of Recommendation	Certainty of Evidence
Maintenance therapy with antipsychotic medicine for a minimum of 7–12 months should be offered in adults with a first episode of psychosis (including schizophrenia) in remission, carefully balancing effectiveness, side-effects, and individual preference. Justification • After performing a literature search, evidence was extracted from 3 systematic reviews: Ceraso et al (75 RCTs on maintenance treatment with antipsychotic medicines in schizophrenia),[15] Kishi et al (10 RCTs on discontinuation versus maintenance of antipsychotic medicines in schizophrenia),[23] and Schneider-Thoma et al (596 RCTs on serious adverse events and mortality of second-generation antipsychotic medicines).[17] • Maintenance therapy was significantly superior to discontinuation with a follow-up of up to 12 months as well as up to 24 months.[23] Remarks • Discontinuation of antipsychotics should always be done by gradually and slowly reducing the medicine dose. When medicines are discontinued, people living with schizophrenia and family members need to be educated to detect the reemergence of symptoms early to allow for close clinical monitoring of relapse. Implementation considerations • Treatment with antipsychotic medicines should be combined with psychosocial interventions (see PSY10 and PSY11). • Interruptions in medicine availability (common in LMICs and in supply chain interruption such as during emergencies) may interfere with continuation of treatment. Reliability of supply should inform choice of medicine. • For the treatment of psychotic disorders, the WHO EML[18] includes: - fluphenazine (therapeutic alternatives: haloperidol decanonate, zuclopenthixol decanonate) - haloperidol (therapeutic alternative: chlorpromazine) - haloperidol injection - olanzapine - paliperidone (therapeutic alternative: risperidone injection) - risperidone (therapeutic alternatives: aripiprazole, olanzapine, paliperidone, quetiapine) - complementary list: clozapine. Research gaps • There was no evidence for maintenance therapy for more than 2 years and evidence was scarce between 1- and 2-year follow-up. More studies are required on longer-term maintenance therapy.	**Strong**	**Moderate**
Previous Recommendation 2012		
Recommendation(s)	Strength of Recommendation	Certainty of Evidence
In individuals with a first psychotic episode with full and sustained remission, antipsychotic treatment should be continued for at least 12 months after the beginning of remission. Any further continuation of antipsychotic drug treatment should be based on clinical review preferably by a mental health specialist and taking into account the preferences of the individuals, in consultation with the family.	Strong	Very low
Note: Strength of recommendation: strong or conditional according to GRADE; quality of evidence: very low, low, moderate, or high. Underlying evidence 2023[15,17,23]; underlying evidence 2012.[24] Source updated recommendation and comments[14]; source recommendation from 2012.[22] The justification, remarks, implementation considerations, and research gaps were developed in cooperation between the Guideline Development Group, the External review group, and the systematic review team. The updated recommendations are highlighted in bold and only these are discussed in the main text. The previous versions of updated recommendations are also shown (shaded in gray), to see how the recommendations have changed during the update process.		
Key question PSY4: In adults with psychotic disorders (including schizophrenia) requiring long-term treatment, what is the safety and role of depot antipsychotic medicine?		
Updated Recommendation 2023 (PSY4)		
Recommendation(s)	Strength of Recommendation	Certainty of Evidence
Long-acting injection (LAI) antipsychotic medicines—namely fluphenazine, haloperidol, paliperidone, risperidone, and zuclopenthixol—should be considered as an alternative to oral antipsychotic medicines for adults with psychotic disorders (including schizophrenia) requiring long-term treatment, carefully balancing effectiveness, side-effects, and personal preference.	**Conditional**	**Moderate**

Table 1. Continued

Key question PSY4: In adults with psychotic disorders (including schizophrenia) requiring long-term treatment, what is the safety and role of depot antipsychotic medicine?		
Updated Recommendation 2023 (PSY4)		
Recommendation(s)	Strength of Recommendation	Certainty of Evidence
Justification • After performing a literature search, evidence was extracted from 2 systematic reviews Kishimoto et al (32 RCTs, 65 cohort studies, and 40 pre-post studies on long-acting injectable (LAI) vs oral antipsychotics for the maintenance treatment of schizophrenia)[25] and Schneider-Thoma et al (132 RCTs on comparative efficacy and tolerability of 32 oral and LAI antipsychotics for the maintenance treatment of adults with schizophrenia).[26] • Almost all LAIs compared with placebo had large effects for relapse prevention. Remarks • The medicines included in the recommendation correspond to the WHO EML.[18] The above recommendation is based on the context, availability, and costs of using long-acting injectables. Implementation considerations • With depot antipsychotic medication, compliance of people living with psychotic disorders with treatment plans can be improved. • People living with long-term psychotic disorders should be involved in medicine choice in a supported decision-making process, without coercion and in line with human rights instruments. • Treatment with antipsychotic medicines should be combined with psychosocial interventions (see PSY11). Research gaps • Most of the evidence is from high-income countries. • More trials comparing second-generation long-acting injectables head-to-head, and first-generation antipsychotics to second-generation antipsychotics are needed.		
Previous Recommendation 2012		
Recommendation(s)	Strength of Recommendation	Certainty of Evidence
In people with psychotic disorder (including schizophrenia) requiring long-term antipsychotic treatment, depot antipsychotics can be offered instead of oral medications as part of a treatment plan.	Conditional	Very low
Note: Strength of recommendation: strong or conditional according to GRADE; quality of evidence: very low, low, moderate, or high. Underlying evidence 2023[25,26]; underlying evidence 2012.[27,28] Source updated recommendation and comments[14]; source recommendation from 2012.[22] The justification, remarks, implementation considerations, and research gaps were developed in cooperation between the Guideline Development Group, the External review group, and the systematic review team. The updated recommendations are highlighted in bold and only these are discussed in the main text. The previous versions of updated recommendations are also shown (shaded in gray), to see how the recommendations have changed during the update process.		
Key question PSY5: Is antipsychotic medicine effective and safe for adolescents with psychotic disorders (including schizophrenia)?		
Updated Recommendation 2023 (PSY5)		
Recommendation(s)	Strength of Recommendation	Certainty of Evidence
5.1 Oral antipsychotic medicines—namely aripiprazole, olanzapine, paliperidone, quetiapine, risperidone—should be considered under specialist supervision for adolescents with psychotic disorders (including schizophrenia), carefully balancing effectiveness, side-effects, and individual preference.	**Conditional**	**Low**
5.2 Clozapine should be considered for adolescents with a treatment-resistant psychotic disorder (including schizophrenia) under specialist supervision, carefully balancing effectiveness, side-effects, and individual preference.	**Conditional**	**Low**
Justification • After performing a literature search, data were extracted from a network-meta-analysis on efficacy, acceptability, and tolerability of antipsychotics in children and adolescents with schizophrenia: Krause et al (28 RCTs).[29] Remarks • The medicines included in the recommendation correspond to the WHO EML[18] and are listed in alphabetical order. • Clozapine should only be offered where laboratory tests are available to monitor white blood cell count, and under a mental health specialist supervision.		

Table 1. Continued

Key question PSY5: Is antipsychotic medicine effective and safe for adolescents with psychotic disorders (including schizophrenia)?		
Updated Recommendation 2023 (PSY5)		
Recommendation(s)	Strength of Recommendation	Certainty of Evidence
Implementation considerations • Only a few antipsychotics are officially licensed for children and adolescents, which should be considered in medicine choice, taking into account the country and context. • Antipsychotic medicine should be considered for adolescents with psychotic disorders only under supervision of a mental health specialist. • Adolescents are more susceptible to side-effects from antipsychotic medicines than adults. In turn, during the clinical decision-making process, adolescents living with psychosis should be made aware of benefits and side-effects so that they are able to make informed choices regarding the treatment plan. Additionally, carer preference should be taken into consideration. • Furthermore, given the higher susceptibility of adolescents to side-effects, the medicines approved in a given country should be carefully considered before formulating a treatment plan. Research gaps • Insufficient knowledge of long-term side-effects in adolescents.		
Previous Recommendation 2012		
Recommendation(s)	Strength of Recommendation	Certainty of Evidence
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.	Conditional	Very low
Note: Strength of recommendation: strong or conditional according to GRADE; quality of evidence: very low, low, moderate, or high. Underlying evidence 2023[29]; underlying evidence 2012.[31–34] Source updated recommendation and comments[14]; source recommendation from 2012.[22] The justification, remarks, implementation considerations, and research gaps were developed in cooperation between the Guideline Development Group, the External review group, and the systematic review team. The updated recommendations are highlighted in bold and only these are discussed in the main text. The previous versions of updated recommendations are also shown (shaded in gray), to see how the recommendations have changed during the update process.		
Key question PSY10: In adults with psychotic disorders (including schizophrenia), are psychological interventions (such as psychoeducation, family interventions, and cognitive behavioural therapy) effective in the acute phase?		
Updated Recommendation 2023 (PSY10)		
Recommendation(s)	Strength of Recommendation	Certainty of Evidence
Treatment based on cognitive behavioural therapy (CBT) should be considered for adults with psychotic disorders (including schizophrenia) in the acute state of the condition where sufficient specialist support is available. Justification • Data were extracted from a network-meta-analysis: Bighelli et al (53 RCTs on the use of 7 psychological interventions to reduce positive symptoms in schizophrenia).[36] • Cognitive behavioural therapy (CBT) was significantly superior to treatment as usual (TAU) for the outcomes overall symptoms, quality of life, and functioning. • The certainty of evidence was moderate for CBT for overall symptoms and very low to low for the other outcomes. Remarks • Integrating the provision of psychological interventions into primary care provision and other general and social care facilities has many advantages, including more holistic healthcare, increased accessibility for people in need of mental healthcare, opportunities for reducing the stigma of mental health problems and reduced costs. Implementation considerations • CBT requires specific training, which may not be available in all low- and middle-income countries. • Differences in mental health infrastructure and resources should be considered as well as variations in cultural context—there may be acceptability issues. • Country adaptation and translation of training materials and tools for the provision of psychological interventions is essential. • Face-to-face psychological interventions delivered by service providers is human resource-intensive as they require substantial provider time, training, and supervision.	**Conditional**	**Moderate**

Table 1. Continued

Key question PSY10: In adults with psychotic disorders (including schizophrenia), are psychological interventions (such as psychoeducation, family interventions, and cognitive behavioural therapy) effective in the acute phase?		
Updated Recommendation 2023 (PSY10)		
Recommendation(s)	Strength of Recommendation	Certainty of Evidence
Research gaps • Most of the research is from high-income countries and, in general, psychological interventions have been developed there. Further research is needed in low- and middle-income countries. • Further research is needed on psychoeducation or family interventions focused on individuals in the acute phase of the disease.		
Previous Recommendation 2012		
Recommendation(s)	Strength of Recommendation	Certainty of Evidence
Psychoeducation should be routinely offered to individuals with psychotic disorder (including schizophrenia) and bipolar disorders and their family members/caregivers.	Strong	Very low
For individuals with psychotic disorders (including schizophrenia) and bipolar disorder, cognitive behavioural therapy, and family interventions can be considered as an option if adequate trained professionals are available. Professionals delivering these interventions should have an appropriate level of competence and, wherever possible, be regularly supervised by the relevant specialists. These 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. Individuals and families should be actively involved in the design, implementation, and evaluation of these interventions in coordination with health and social professionals.	Conditional	Very low
Note: Strength of recommendation: strong or conditional according to GRADE; quality of evidence: very low, low, moderate, or high. Underlying evidence 2023[36]; underlying evidence 2012: Psychoeducation[37,38]; Family therapy[39,40]; Cognitive behavioural therapy.[38,41,42] Source updated recommendation and comments[14]; source recommendations from 2012.[22] The justification, remarks, implementation considerations, and research gaps were developed in cooperation between the Guideline Development Group, the External review group, and the systematic review team. The updated recommendations are highlighted in bold and only these are discussed in the main text. The previous versions of updated recommendations are also shown (shaded in gray), to see how the recommendations have changed during the update process.		
Key question PSY11: In adults with psychotic disorders (including schizophrenia) are psychological interventions (such as psychoeducation, family interventions, and CBT) effective in the maintenance phase?		
New Recommendation 2023 (PSY11)		
Recommendation(s)	Strength of Recommendation	Certainty of Evidence
Psychosocial interventions—namely family interventions, family psychoeducation, psychoeducation, and cognitive behavioural therapy (CBT)—should be offered to adults with psychosis (including schizophrenia) during the maintenance phase, either alone or in combination.	**Strong**	**Moderate**
Justification • Data were extracted from a network-meta-analysis: Bighelli et al (72 RCTs on the use of psychosocial and psychological interventions for relapse prevention in schizophrenia).[43] • Most of the psychological interventions were significantly superior to treatment as usual for relapse prevention. Cognitive behavioural therapy, family intervention, and relapse prevention programs showed large effects. Family psychoeducation, integrated intervention, and psychoeducation showed medium effects. Remarks • Although, as described under justifications, many psychosocial interventions had beneficial effects in maintenance therapy, the efficacy of family interventions, family psychoeducation, and CBT were most robust.[43] Moreover, a subsequent analysis examining only family interventions found that simple family psychoeducation is the most recommendable one. Implementation considerations • Not all forms of psychological interventions may be available in low- and middle-income countries. • Attempts should be made to involve family and carers in maintenance treatment. • Family psychoeducation, a relatively simple intervention that has been proven effective, should be offered in all settings. • Variations in cultural context should be considered. There may be acceptability issues. • Integrating the provision of psychological interventions into primary care provides many advantages, including more holistic healthcare, increased accessibility of mental health services for people in need of care, opportunities for reducing the stigma of mental health problems and reduced costs.		

Table 1. Continued

Key question PSY11: In adults with psychotic disorders (including schizophrenia) are psychological interventions (such as psychoeducation, family interventions, and CBT) effective in the maintenance phase?		
New Recommendation 2023 (PSY11)		
Recommendation(s)	Strength of Recommendation	Certainty of Evidence
Research gaps • Most of the research is from high-income countries and, in general, psychological interventions have been developed there. Further research is needed in low- and middle-income countries. • Many interventions have so far been investigated in only a few trials and individuals, and thus deserve further study. *Note*: Strength of recommendation: strong or conditional according to GRADE; quality of evidence: very low, low, moderate, or high. Underlying evidence 2023.[43] Source updated recommendation and comments.[14] The justification, remarks, implementation considerations, and research gaps were developed in cooperation between the Guideline Development Group, the External review group, and the systematic review team. The updated recommendations are highlighted in bold and only these are discussed in the main text. The previous versions of updated recommendations are also shown (shaded in gray), to see how the recommendations have changed during the update process.		

Source: Ref. [44]

Each updated recommendation is based on 1 key question in the PICO format (for more detailed information regarding each key question, please see appendix table 1):

- *PSY1*: In adults with psychotic disorders (including schizophrenia) are antipsychotic medicine safe and effective?
- *PSY2*: In adults with a first psychotic episode (schizophrenia) with full remission, how long should antipsychotic medicine be continued after remission in order to allow for the best outcomes?
- *PSY4*: In adults with psychotic disorders (including schizophrenia) requiring long-term treatment, what is the safety and role of depot antipsychotic medicine?
- *PSY5*: Is antipsychotic medicine effective and safe for adolescents with psychotic disorders (including schizophrenia)?
- *PSY10*: In adults with psychotic disorders (including schizophrenia) are psychological interventions (such as psychoeducation, family interventions, and cognitive behavioral therapy) effective in the acute phase?
- *PSY11*: In adults with psychotic disorders (including schizophrenia) are psychological interventions (such as psychoeducation, family interventions, and CBT) effective in the maintenance phase?

In addition, the conclusions to each updated recommendation including (1) justification (the evidence behind the recommendations), (2) remarks (providing some additional explanations for utilization of the recommendations), (3) implementation considerations (various aspects that are influencing the implementation of the guideline), and (4) research gaps are presented (a summary is presented in table 1; detailed information is available from WHO[14]).

WHO uses the expression psychoses (including schizophrenia), to not only include people living with schizophrenia, but all those affected by psychoses in general.

PSY1: Safety and Efficacy of Antipsychotics in Adults With Psychotic Disorders

The current guideline strongly recommends the following antipsychotics: aripiprazole, chlorpromazine, haloperidol, olanzapine, paliperidone, quetiapine, and risperidone.[14] In the previous recommendation, there was a strong recommendation for haloperidol and chlorpromazine for individuals living with psychotic disorders (including schizophrenia), and a conditional recommendation for second-generation antipsychotics as an alternative, yet no specific second-generation antipsychotics were mentioned.[22] For the guideline update, evidence was extracted from 3 systematic reviews: Ceraso et al,[15] Leucht et al,[16] and Schneider-Thoma et al.[17] The updated evidence showed small differences in efficacy between the antipsychotics with low certainty evidence, whereas differences in side effects were more distinct with very low to low certainty evidence.[13,16] The 2023 updated recommendation was aligned with the WHO List of Essential Medicines (EML), which was updated in parallel. Before the EML update, the only second-generation antipsychotic included was risperidone (however, risperidone was not explicitly recommended in the previous 2012 recommendation). In 2023 aripiprazole, olanzapine, paliperidone, and quetiapine were added as therapeutic alternatives to risperidone to the EML,[45] and the updated guideline recommendation now explicitly recommends these second-generation antipsychotics in adults with psychotic disorder.[14]

The recommendation is a compromise between the evidence of the 3 selected studies[15–17] and the alignment with the EML (more details regarding the alignment with the EML are provided in the discussion). The purpose of the compromise is to ensure the enhancement of access to medication, that are affordable and cost-effective including in low- and middle-income countries, which are

one of the key target audiences of the mhGAP guidelines and its derivative products. Please refer to table 1 (key question PSY1) for more details.

PSY2: Duration of Pharmacotherapy in First Episode Psychosis

The current guideline recommends maintenance therapy for a minimum of 7–12 months in adults with a first episode of psychosis (including schizophrenia) in remission,[14] whereas the previous guideline in 2012 recommended maintenance therapy for the first episode psychosis for at least 12 months. The updated evidence showed high certainty evidence for maintenance therapy between 7 and 24 months, however, follow-up data were scarce between 1- and 2-year follow-up.[13,15] In addition to the evidence, the decision for the recommended timeframe was taken against the background of various side effects of the antipsychotics. Moreover, in the first episode psychosis, it is frequently uncertain whether the diagnosis of schizophrenia is fulfilled or if it is a time-limited psychosis that will not develop into schizophrenia.[46] After considering these aspects, maintenance therapy for a minimum of 7–12 was recommended, and not up to 2 years.

As a remark to this recommendation, it is stated that antipsychotics should be discontinued by gradually and slowly reducing the dosage. Moreover, when medicines are discontinued, people living with schizophrenia and family members need to be educated to detect the reemergence of symptoms early to allow for close clinical monitoring of relapse.[14] Please refer to table 1 (key question PSY2) for more details.

PSY4: Safety and Role of Depot Antipsychotic Medicine

The updated guidelines recommend specific depot antipsychotics fluphenazine, haloperidol, paliperidone, risperidone, and zuclopenthixol, whereas in 2012, there was a general recommendation for depot antipsychotics without mentioning specific antipsychotics. The updated recommendations correspond to the WHO EML, which includes depot antipsychotics.[18] Depot antipsychotics are recommended as the adherence of people living with psychotic disorders can be improved. This is relevant as up to 50% of people living with psychosis are nonadherent.[47,48] Of particular importance is the involvement of people with long-term psychoses in medicine choice in a shared decision-making process and in line with human rights instruments, and there should not be any form of coercion. With adding this implementation consideration, the WHO emphasizes its commitment to its constitution and the upholding of human rights, which must be integrated into recommendations and guidelines (see "From evidence to recommendations" section). The alignment of Member States mental health, policies, plans, and laws with international human rights instruments is a component of the WHO Comprehensive Mental Health Action Plan 2013–2030, under its global targets 1.1 and 1.2 formally endorsed by all WHO Member States in its Seventy Fourth World Health Assembly.[49] The Member States are committed to report on this alignment with international human rights instruments every 2 years to WHO through WHO Mental Health Atlas.[50]

Some patients having received depot antipsychotics are considering it as a compulsory treatment and have a fear to lose autonomy.[44,51] The GDG expressed concerns that depot antipsychotics more than oral antipsychotics may have the risk of being given forcibly against the consent of the patient. Therefore, patients should receive comprehensible information about the use and possible side effects of depot antipsychotics compared with oral medication. This shared decision-making may have long-term positive treatment effects, as the acceptance of depot antipsychotics by patients frequently increases with experience.[44] Please refer to table 1 (key question PSY4) for more details.

PSY5: Safety and Efficacy of Antipsychotic Medicine in Adolescents With Psychotic Disorders (Including Schizophrenia)

There was a joint recommendation on the efficacy and safety of pharmacological interventions in adolescents for both schizophrenia and bipolar disorder in 2012. In 2023, the update process of the mhGAP guidelines resulted in 2 separate recommendations, 1 for schizophrenia and 1 for bipolar disorder (PSY6, not discussed in this article). In alignment with the updated EML, paliperidone was added, whereas ziprasidone is not recommended in the updated recommendation.[14] Clozapine, with its potentially serious side effects, has now been included in the recommendation for adolescents with treatment-resistant psychotic disorder. Specialist supervision is recommended, although this will not always be feasible in contexts with limited mental health resources. There are few antipsychotics licensed for adolescents and in turn, there may be a discrepancy between the guideline recommendation and the officially available medicines in a given country, which should be taken into account when choosing medications. For example, clozapine is approved for adolescents with early-onset schizophrenia older than 16 years by the European Medicines Agency, whereas it is nonapproved by the Food & Drugs Administration.[30] Please refer to table 1 (key question PSY5) for more details.

PSY10: Efficacy of Psychological Interventions in the Acute Phase

The guideline update process resulted in 3 separate recommendations: psychological interventions in the acute

state of schizophrenia (PSY10), psychological interventions in the maintenance phase of schizophrenia (PSY11), and psychological interventions for bipolar disorder in remission (PSY12, not discussed in this article). In 2012, there was a single joint recommendation for both schizophrenia and bipolar disorder with a strong recommendation for psychoeducation, and conditional recommendation for cognitive behavioral therapy (CBT), and family interventions.[22] The updated guideline includes a conditional recommendation for CBT, based on moderate certainty in the evidence.[14,36] However, a note is included along with the recommendation that this only applies if sufficient specialist support is available.

It should be noted that in addition to the 2 WHO guideline recommendations on psychosocial interventions (PSY10 and PSY11), most of the recommendations on antipsychotics have a remark to combine antipsychotics with psychosocial interventions. Despite this recommendation, there may be feasibility problems, particularly in LMICs, which is also noted in the implementation considerations of PSY10 and PSY11. CBT for schizophrenia requires specific training, is human resource-intensive, needs a strong mental health infrastructure, and may not be accepted in all countries due to variations in cultural context.[14] Regarding further research it would be important to investigate whether there is a benefit of more technical forms of therapy (eg, CBT) over interventions that could be more easily scalable globally with less human or financial resources (eg, befriending). In high-income countries, providing psychotherapy to every patient may also be challenging and is not always feasible. Please refer to table 1 (key question PSY10) for more details.

PSY11: Efficacy of Psychological Interventions in the Maintenance Phase

Regarding the efficacy of psychological interventions in the maintenance phase, a new key question and recommendation was developed, as there was no previous recommendation. Besides CBT, 3 forms of psychotherapy are recommended: family interventions, family psychoeducation, and psychoeducation. Although these interventions are overlapping in content, the evidence highlighted medium to large effect sizes for relapse prevention. Other forms of psychological interventions (eg, relapse prevention programs, integrated interventions) also had beneficial effects on relapse prevention, however, the efficacy of family interventions, family psychoeducation, and CBT remained robust in various subgroup analyses.[43] In addition, a subsequent analysis examining only family interventions found that family psychoeducation is the most recommendable form of psychological intervention. This is important to note as family psychoeducation is the simplest form of psychotherapy, but nevertheless the most effective, and should be the minimum standard of care with psychotherapy even in LMICs. Please refer to table 1 (key question PSY11) for more details.

Discussion

During the WHO guideline for psychoses update in 2023, 6 out of 12 recommendations from 2015 were updated and 1 recommendation was newly developed, resulting in an updated guideline that includes 13 recommendations. There are a number of distinct elements in the development of mhGAP that differentiate it from national guidelines. Additionally, an outlook on potential improvements of the guideline is provided.

Evidence-based guidelines are an essential part of the WHO mhGAP.[2] WHOs update on recommendations for psychoses will help to ensure access to evidence-based treatment for patients across the globe. The WHO guideline development process and the formulated recommendations themselves differ significantly from comparable national guidelines, such as the American Psychiatric Association Professional Practice Guidelines, the German S3 Guideline for Schizophrenia, or the British NICE guideline for schizophrenia.[52–54] The WHO offers only 13 key questions and recommendations for psychoses, whereas eg, the German schizophrenia guideline includes 162 recommendations. The reason is that the recommendations are limited to particularly essential and transnational topics (eg, safety and efficacy of antipsychotics, duration of antipsychotic treatment), so that they are applicable across various countries, which can then adjust them according to their respective regularities of the health system. Despite the rather general treatment recommendations, specific medications are mentioned in the WHO guideline, which is not common in the mentioned national guidelines for schizophrenia, whose target group is primarily healthcare specialists in high-income countries with sufficient medication supply. Since the WHO guideline is intended for use globally, including LMICs and nonspecialized healthcare settings, the recommended medications are aligned with the EML.

The 2023 WHO guideline update process ran in parallel with the WHO EML update process, which provided an opportunity to harmonize the 2 documents.[45] The evidence supported the medications being recommended for the EML, and this aspect was taken into consideration by the GDG when formulating the recommendations. However, solely considering the evidence, recommendations with specific medications may not have been suggested, as the investigated antipsychotics were similarly effective.[16,26] Yet, the WHO guideline development process is not based solely on evidence, but also takes strategic issues and contextual factors into consideration, with the primary goal of ensuring implementation in LMICs. This implicates that although the evidence is the same, the GRADE process might lead to somewhat different recommendations depending on the emphasis of different contextual elements according to the target of guidelines and the setting of their application. The WHO EML specifies certain medications as essential medicines and emphasizes

the importance that availability and affordability should be ensured by all governments.[55] As many LMICs assemble their national medication lists based on the EML, limited healthcare in many nations may be a concern if the EML only provides a few options for medications (eg, solely risperidone as a second-generation antipsychotic prior to the recent update) due to the varying tolerability of antipsychotics among individuals.[26] The guideline recommendations harmonized with the WHO EML, can improve guideline uptake and implementation in LMICs.

Overall, more evidence on older first-generation antipsychotics would be desirable in the context of LMICs. The fact that more second-generation antipsychotics are recommended in the WHO guideline is also due to the low quality of evidence for older medications except haloperidol.[56] Considering the lower cost of these medications and likely availability problems of newer second-generation medications, more evidence on relevant older antipsychotics could enhance the healthcare for people living with psychoses in lower- and middle-income countries.

Regarding the recommendation of duration of pharmacotherapy in first episode psychosis, the WHO guideline recommends maintenance therapy for a minimum of 7–12 months. Other national schizophrenia guidelines, such as the German S3 guideline or the NICE guideline, do no longer specify a duration for maintenance therapy, but emphasize the importance of shared decision-making and the inclusion of different external and individual factors.[52,54] It is important to note, that in LMICs, follow-up models and specialist healthcare are often not available, and continuous psychosocial support is frequently not guaranteed. Therefore, a treatment recommendation over a defined minimum period of 7–12 months is important even in first episode psychosis, although some patients (about 12%–22%[46]) with a time-limited single episode of psychosis could possibly be overtreated.

In summary, a strength of the WHO mhGAP guidelines is the systematic and transparent guideline development process by using the GRADE methodology, while other national guidelines for schizophrenia, except for the NICE guideline, do not apply the GRADE methods. The evidence appraisal for all selected outcomes and reasons for downgrading is available in the evidence profiles, along with the aspects considered by the GDG when going from the evidence to recommendations (eg, values and preferences, benefits and harms, equity). In addition, a key strength of the WHO mhGAP guidelines is that an evidence-based guideline based on a few key recommendations can be developed and implemented in more than 100 countries, and be general enough to fit into their health systems and policies, while still working toward minimizing the treatment gap. Moreover, the WHO mhGAP guidelines (and the EML) point out the best available evidence which might improve mental health globally. Subsequently, this could stimulate scientists, manufacturers, global health and social care organizations, and policymakers, potentially favoring an increased availability and accessibility of interventions.

For potential future updates of the mhGAP WHO guidelines on psychoses (as well as for the whole WHO mhGAP guidelines), the aspect of improving shared decision-making and the possibility of converting it into a living guideline should also be explored. As per the GRADE methods for guideline development followed by WHO, the decision-making process is meant to include consideration of patients' values and preferences. However, evidence on patients' values and preferences is usually scarce, and individual patients may hold different values and preferences compared with those of the clinician, guideline panel, or other patients.[57] This is especially true for GRADE conditional recommendations, given the variability of choices among patients, which need guidance to make decisions in accordance with their values and preferences (see appendix table 2).

Decision aids could bridge this gap through presenting the patient with comprehensible information regarding the recommended intervention's evidence, benefits, and harms, allowing for an informed decision. Yet many decision aids are outdated and not utilized in clinical practice.[58] This can also be observed with guidelines, which are often out of date by the time they are published.[59–61] The previous update to the WHO guidelines on psychoses was in 2014, and since then, there has been a significant amount of new evidence, however, 9 years have passed before a new guideline update was released. One possible solution is to convert the mhGAP WHO guideline on psychoses into a living guideline. Living guidelines permit the update of individual recommendations upon the emergence of new and relevant evidence.[59] Thereby, only parts of the guideline will be updated as required and not the entire guideline, which is a time-intensive process. This requires that the guideline is digitalized in an evidence ecosystem, such as MAGICapp, a digital authoring and publication platform that allows authors to develop and publish (living) guidelines.[62] The evidence ecosystem MAGICapp allows the semi-automatic creation of visual depictions of the evidence, which can serve as decision aids during a shared decision-making process.[35,63] The WHO already has a living guideline for COVID-19 treatment using MAGICapp. Transforming the mhGAP guideline on psychoses into a digitalized living guideline with linked decision aids could ensure that patients living with schizophrenia receive treatment according to the current state of the art as well as enhance the dissemination and guideline uptake, resulting in a marked improvement in the treatment of patients with schizophrenia.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

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Author Contributions

All authors made substantial contributions to the conception of the work and drafting of the work, gave approval for publication, and agreed to be accountable for the work.

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