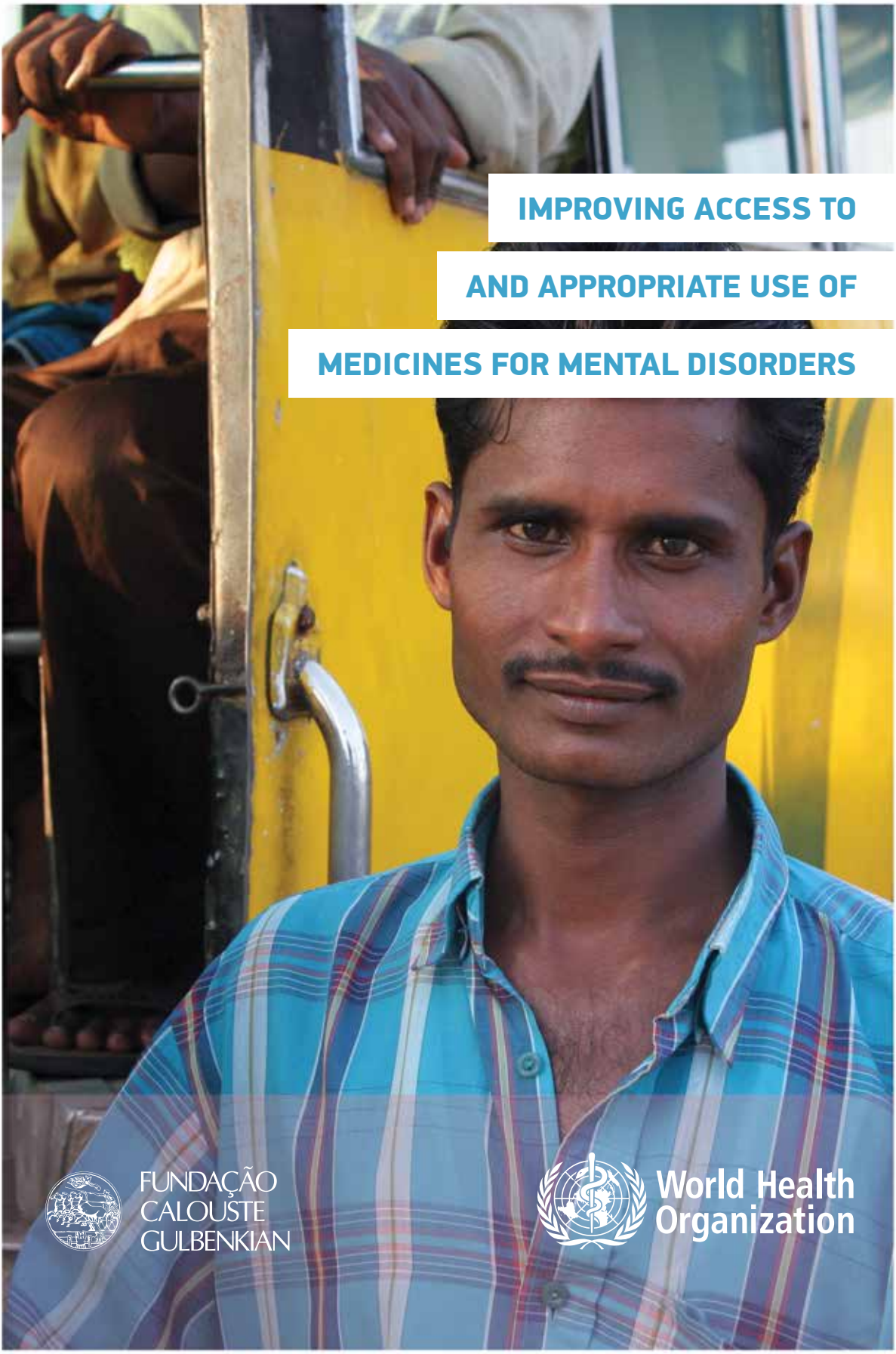

IMPROVING ACCESS TO AND APPROPRIATE USE OF MEDICINES FOR MENTAL DISORDERS

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World Health Organization

Improving access to and appropriate use of medicines for mental disorders.

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IMPROVING ACCESS TO AND APPROPRIATE USE OF MEDICINES FOR MENTAL DISORDERS

This publication is part of a series of thematic papers, co-produced by the World Health Organization and the Calouste Gulbenkian Foundation's Global Mental Health Platform. To date, the series covers the following topics.

- Innovation in deinstitutionalization: a WHO expert survey
- Integrating the response to mental disorders and other chronic diseases in health care systems
- Social determinants of mental health
- Promoting rights and community living of children with psychosocial disabilities
- Improving access to and appropriate use of medicines for mental disorders.

Examples from different countries are used throughout this report to illustrate some of the key issues, problems and solutions in relation to access to medicines for mental disorders. The information and data contained in the report are drawn from published sources that cannot be verified independently. The use of examples does not imply that these issues, problems and solutions are unique to a specific country.

The examples should not be viewed as an assessment of countries' overall performance in relation to access to medicines: they are used for illustrative purposes only and apply to many countries around the world.

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FOREWORD

As awareness of the importance of mental health increases, international organizations face the challenge of providing evidence-based guidance and good practices to assist countries in the provision of mental health care.

The Gulbenkian Global Mental Health Platform and the World Health Organization (WHO) have collaborated to generate information to help meet this challenge, publishing a series of thematic papers on pressing mental health issues of our time. One of these thematic papers, *Integrating the response to mental disorders and other chronic diseases in health care systems*, emphasised that mental health systems should "ensure the availability of essential medicines at all levels of the health system (and allow trained, non-specialist providers to prescribe them)". This concept refers to the issue of improving access to a selected range of medicines for mental disorders and implementing appropriate prescribing policies.

This is entirely consistent with the Sixty-seventh World Health Assembly resolution on access to essential medicines, which urged Member States to improve national policies for the selection of essential medicines and to promote their availability, affordability and appropriate use. The Comprehensive Mental Health Action Plan adopted by the Sixty-sixth World Health Assembly emphasized the need to "procure and ensure the availability of basic medicines for mental disorders included in the WHO List of Essential Medicines at all health system levels" and to "ensure their rational use".

The present document attempts to provide simple, adequate and evidence-based information to policy-makers, public health professionals and prescribers, especially in low- and middle-income countries, to improve access to and appropriate use of medicines for mental disorders. It is hoped that use of this thematic paper will enhance the knowledge and competence of those health professionals who are at the forefront of mental health service organization and delivery of care in resource-poor health systems. This will facilitate much needed scaling-up of services for people with mental, neurological and substance use disorders.

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Corrado Barbui (WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation, University of Verona, Verona, Italy) and Tarun Dua (WHO Department of Mental Health and Substance Abuse) coordinated this thematic paper under the overall direction of Shekhar Saxena (WHO Department of Mental Health and Substance Abuse) and Benedetto Saraceno (Calouste Gulbenkian Foundation).

This thematic paper was written by Corrado Barbui and Tarun Dua. Extensive input was received from Kavitha Kolappa (Massachusetts General Hospital/McLean Psychiatry Residency, Harvard University). An advisory panel of international experts commented and contributed on various subtopics. Contributions were integrated into a full draft, which then underwent a further round of review, discussion, revision and finalization. We are thankful to Grazia Motturi for the support provided for the development and publication of the report.

Expert panel members (listed below) contributed to the report and reviewed it at various stages of development.

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EXECUTIVE SUMMARY

BACKGROUND

Mental disorders account for a significant proportion of the total global burden of disease and are the leading cause, worldwide, of years lived with disability.

The resources allocated to addressing mental disorders have thus far been grossly inadequate, inequitably distributed and inefficiently used. The result is a large treatment gap, with more than 75% of people in low- and middle-income countries (LMICs) having no access to mental health services. In many LMICs, overburdened health systems are often unable to provide even the most basic mental health care, including medicines to treat mental disorders.

Broadly defined, access to medicines for mental disorders (or psychotropic medicines) encompasses rational selection, availability, affordability and appropriate use of those medicines. Barriers to ensuring access to psychotropic medicines exist at all levels of the health-care system: international; national or subnational (state or provincial); district; community, household or individual.

PURPOSE

This report is intended for use by policy-makers, public-health professionals and prescribers working in national health ministries, in subnational health offices, or at the district level and in charge of planning improvements to mental health systems. It includes practical instructions for the appropriate use of psychotropic medicines by health-care professionals working in LMICs.

The specific aims of the report are thus threefold:

- to examine current barriers to access to psychotropic medicines;
- to identify key priority actions at all levels of the health-care system (international; national or subnational; district; community, household or individual) for improving access to psychotropic medicines, particularly in LMICs;
- to provide health-care professionals, especially in LMICs, with simple and evidence-based information that will enable them to provide pharmacological treatment to people with mental disorders.

METHODOLOGY

The Gulbenkian Global Mental Health Platform, an initiative of the Calouste Gulbenkian Foundation jointly conducted with the Department of Mental Health of the Faculty of Medical Sciences, NOVA University of Lisbon, has developed a series of thematic papers on the pressing mental health issues of our time, with the technical collaboration of the World Health Organization (WHO) Department of Mental Health and Substance Abuse. This is the fifth such report. Throughout development of the report, a scientific secretariat worked closely with an advisory panel of international experts in the fields of access

to medicines, health systems and services research, health policy development, health economics, integrated care implementation, clinical psychopharmacology and pharmacoepidemiology.

CURRENT BARRIERS TO ACCESS TO MEDICINES FOR MENTAL DISORDERS

Many of the barriers to access are applicable to medicines for all diseases and have been extensively studied; some, however, are specific to psychotropic medicines, and are the result of stigma associated with mental disorders, duration and cost of treatments, and the limitations of available research. Barriers to access relating to medicines for mental disorders can be considered to affect primarily either the demand for or the supply of psychotropic medicines.

The *demand* for psychotropic medicines is affected by: the acceptability of mental health treatments and/or awareness of mental health problems within communities; reduced help-seeking behaviour by individuals because of stigma, discrimination or other sociocultural factors; poor recognition that mental disorders are responsive to effective treatment; poor treatment adherence due to a number of factors, including side-effects and the long-term nature of many severe mental disorders and resultant implications for duration and cost of services; and, in many areas, geographical distance from health-care providers.

The *supply* of psychotropic medicines can be particularly challenging. The low level of current use of these medicines may lead those responsible for the supply chain to believe that true demand is low. Additional impediments include the high costs to health systems and to end users in populations with no financial protection or health insurance, as well as the regulations that govern use of controlled medicines in some countries. Further, the selection of essential medicines and development of robust evidence-based guidelines can be especially difficult for mental disorders, as the evidence on psychotropic medicines has several methodological limitations. The supply of psychotropic medicines can be particularly problematic during humanitarian emergencies, which include a broad range of acute and chronic crises arising from armed conflicts and both natural and industrial disasters.

FRAMEWORK FOR UNDERSTANDING ACCESS TO MEDICINES FOR MENTAL DISORDERS

WHO has developed frameworks for understanding the access pipeline for all medicines. One of the first was developed in 2000 by WHO and Management Sciences for Health and has since been expanded to focus on the following components of access: rational selection, availability, affordability and appropriate use of essential medicines.

- **Rational selection** - refers to the careful selection of medicines based on best available evidence to inform practice and ensure economic viability of health-care systems. From a prescriber and consumer perspective, careful selection reduces duplication and confusion while increasing the chances that side-effects will be monitored and adverse events prevented. Rational selection also allows for a more simplified, efficient approach to training in both prescribing and dispensing. Fur-

ther, it facilitates bulk purchase and easier management of medicines in terms of storage and distribution. Monitoring of medication utilization and quality is also facilitated by rational selection.

- **Availability** - pertains to the obtainability of quality medicines in the public and private sectors. Availability depends upon a number of factors, both distal and proximal to the end user. At national and subnational levels, availability is determined by processes for medicine regulation and functional supply systems, including procurement and distribution chains. At district and community levels, availability of quality medicines is affected by the reliability of health systems and structures, especially in remote and rural areas where the density of providers may be very low. Availability may also be affected by the perception and acceptability of mental health treatment within communities.
- **Affordability** - is determined by the cost of medicines to the health system and to the end user. Even when medicines are physically available, high prices can become a severe constraint for both public health systems and service users. Numerous factors affect the cost of medicines, including intellectual property and patent rights, and the effects of generic competition for medicines, as well as sustainable health financing systems for the public sector.
- **Appropriate use** - refers to the expectation that people receive medicines appropriate to their clinical needs, in doses that meet their individual requirements, for an adequate period of time and at the lowest cost both to them and to the health system. Irrational or inappropriate prescribing, dispensing and use of medicines is a major problem globally. Examples of irrational use of psychotropic medicines include prescribing or dispensing too many medicines per patient (polypharmacy), prescribing inappropriate dosages, poor adherence to correctly prescribed medications, as well as misuse, underuse or overuse.

RECOMMENDATIONS FOR IMPROVING ACCESS TO PSYCHOTROPIC MEDICINES

This report uses an adapted 4 x 4 framework mapping the components of access described above to modifiable factors across four levels of the health system (international; national or subnational; district; community, household or individual). A number of key priority actions for improving access to psychotropic medicines have been identified:

- **International level.** At the international level, rational selection of psychotropic medicines can be facilitated by the development and regular update of medicine lists that satisfy the priority health-care needs of populations in LMICs. Affordability can be enhanced if international and national policies dealing with intellectual property and patent rights provide adequate exemptions for public health needs and to ensure access to medicines. Appropriate use of psychotropic medicines can be improved by the development of robust, evidence-based guidelines at the international level.
- **National or subnational (state or provincial).** Rational selection can be facilitated at the national, state or provincial level through development and maintenance of processes for the selection of medicines, as well as by development and regular update of national essential medicines lists. Availability can be enhanced in a number of ways, including the implementation of reliable supply and quality control systems and the establishment of community-based mental health systems. Affordability can be facilitated by the development of sustainable finance systems in the

public sector. Appropriate use can be improved either by national adaptation of international evidence-based guidelines or by development of national evidence-based guidelines, by monitoring the use of psychotropic medicines and by improving the training of health staff.

- **District level.** At the district level, rational selection can be facilitated by local implementation and adaptation of national or international essential psychotropic medicines lists, as well as by information and education initiatives for health professionals on the national selection process and on local implementation of the national list of essential psychotropic medicines. Availability can be improved by implementation of strategies to provide mental health care in remote and rural areas. More appropriate use can be achieved through education and training initiatives for health staff on critical appraisal of scientific evidence and on use and monitoring of psychotropic medicines.
- **Community, household or individual level.** At the community level, rational selection can be enhanced by the promotion of information and education initiatives on the selection process. Availability can be improved by initiatives that promote the acceptability of mental health treatment and care, including use of medicines. Appropriate use can be enhanced by public education about the role and benefits - as well as the limits and side-effects - of psychotropic medicines. Effective advocacy from service user organizations and coalitions may contribute to improving access to medicines for mental disorders.

CONCLUSION

Access to psychotropic medicines for people with mental illnesses offers the chance of transformative improvement in health and the opportunity for re-engagement in society. By working at all levels of the health system, it is possible to offer this essential component of mental health care to all who can benefit.

INTRODUCTION

The Gulbenkian Global Mental Health Platform is an initiative of the Calouste Gulbenkian Foundation, jointly conducted with the Department of Mental Health of the Faculty of Medical Sciences, NOVA University of Lisbon, which has developed a series of technical reports on the pressing mental health issues of our time, with the technical collaboration of the WHO Department of Mental Health and Substance Abuse. This is the fifth such report.

AIMS AND TARGET AUDIENCE

This report is intended for use by policy-makers, public-health professionals and prescribers working in national health ministries, sub-national health offices or at the district level and in charge of planning improvements to the mental health systems in LMICs. The report is also intended for use by health-care professionals providing pharmacological treatment to people with mental disorders. By analysing the best available evidence, as well as highlighting best practices and the experiences of numerous countries, this report illustrates ways of improving access to and appropriate use of medicines for mental disorders. The term “medicines for mental disorders” are often referred to as “psychotropic medicines”, “psychotherapeutic medicines” or “psychotropics". The specific aims of the report are thus threefold:

- to examine current barriers to access to psychotropic medicines;
- to identify key priority actions at all levels of the health-care system (international; national, sub-national (state or provincial); district; community, household or individual) for improving access to psychotropic medicines, particularly in LMICs;
- to provide health-care professionals, especially in LMICs, with simple and evidence-based information that will enable them to provide pharmacological treatment to people with mental disorders.

This report is therefore of interest to the following groups:

- policy-makers and health planners in the government at national, subnational and local levels;
- members of national mental health departments;
- members of national essential medicines departments;
- clinicians and mental health professionals;
- nongovernmental organizations (NGOs) involved in providing mental health services;
- groups representing people with mental disorders;
- groups representing the families and carers of people with mental disorders;
- advocacy organizations representing the interests of people with mental disorders and their families and carers.

BACKGROUND AND CONTEXT

Mental disorders are responsible for a significant proportion of the total global burden of disease (1) and are the leading cause worldwide of years lived with disability (YLDs).

The resources allocated to addressing mental disorders have thus far been grossly inadequate, inequitably distributed and inefficiently used. The result is a large treatment gap, with more than 75% of people in LMICs having no access to services. In many LMICs, overburdened health systems are often unable to provide even the most basic mental healthcare, including essential medicines to treat mental disorders.

A number of intergovernmental initiatives in recent years have aimed to reduce the treatment gap and enhance the capacity of Member States to improve access to medicines, particularly for mental disorders:

- In May 2013, the Sixty-sixth World Health Assembly adopted WHO's Comprehensive Mental Health Action Plan 2013-2020 (2). The Action Plan recognizes the crucial role of mental health in achieving health for all people and indicates that strategies and interventions for treatment, prevention and promotion need to be based on scientific evidence and/or best practice. The Action Plan builds on the work of WHO's Mental Health Gap Action Programme (mhGAP) (3), the flagship project of which is the development of evidence-based guidelines for mental, neurological and substance use disorders, which include recommendations on appropriate use of medicines for mental disorders.
- In 2014, the Sixty-seventh World Health Assembly adopted a resolution on access to essential medicines (4), which urged Member States to improve national policies for the selection of essential medicines and to promote better medicine availability, affordability, quality, safety and appropriate use.
- In 2015, the Sustainable Development Goals highlighted access to safe, effective, quality and affordable essential medicines as a component of universal health coverage (Goal 3).[1] The aim of universal health coverage is to ensure that all people obtain the health services they need without suffering financial hardship as a result of paying for them (5).

Following the precedent set by these important initiatives, efforts must be made to improve access to essential medicines for mental disorders based on the best available evidence, with appropriate prescribing policies implemented accordingly.

BARRIERS TO ACCESSING MEDICINES FOR MENTAL DISORDERS

Access is generally defined by the timely use of services according to needs (6). Access to medicines, including medicines for mental disorders, is a key component of access to health services and is heavily dependent on the availability and affordability of carefully selected essential medicines. Since the introduction of the essential medicines concept, considerable progress has been made in increasing ac-

[1] *https://sustainabledevelopment.un.org/sdgs*

cess to essential medicines; however, not all people have benefited equally from these improvements. It is estimated that one third of people in LMICs are unable to receive or purchase essential medicines on a regular basis (7).

A recent WHO discussion paper (8) considered the key barriers to access to essential medicines and basic health technologies for noncommunicable diseases (NCDs) and identified the following:

- poor use of health technology assessment in decision-making for selection of medicines;
- poor health systems and supply chain governance;
- excessively strict regulation, particularly of access to some controlled medicines;
- suboptimal utilization of policies on use of generic medicines;
- high price mark-ups and taxes;
- high prices for medicines still under patent;
- poor implementation and use of standard treatment guidelines;
- poor acceptability of treatment by patients, leading to lack of adherence;
- weak civil structures for advocacy and accountability measures for NCD programmes.

Challenges germane to LMICs include inappropriate selection of medicines, poor quality of medicines, interrupted supply chains, high pricing and inadequate financing of medicines (9).

For mental disorders, the prerequisites for improving access to medicines are the availability of services with the capacity to treat those disorders and adequate budget expenditure (10). Globally, mean expenditure for mental disorders is slightly less than 3 percent of the total health budget, and country income levels do not fully account for these low levels of funding. In many LMICs, for example African countries, the number of outpatient health care services with the ability to treat mental disorders is exceedingly low, which is a major infrastructural barrier to appropriate access to and use of medicines.

In addition to these large funding constraints, numerous other barriers - on both the demand side and the supply side - are also particularly relevant to medicines for mental disorders (11). Demand constraints influence the capacity of individuals, households and communities to use services, while supply constraints are aspects of health services and the health sector that hinder service uptake (9).

The demand for psychotropic medicines is affected by: the acceptability of mental health treatments (and/or awareness of mental health problems) within communities; reduced help-seeking behaviour by individuals as a consequence of stigma, discrimination or other sociocultural factors (11, 12); poor recognition of the effectiveness of treatment for mental disorders; poor treatment adherence because of a variety of factors including side-effects, limited insight, cognitive functioning and - given the long-term nature of many severe mental disorders - the implications for duration and cost of services; and, in many areas, geographical distance from health-care providers (13).

The supply of psychotropic medicines can be particularly challenging, as the current low level of use of these medicines may lead those involved in the supply chain to believe that true demand is low. Further impediments include the prohibitive costs to health systems and end users in populations with no financial protection or health insurance, and the regulation of controlled medicines in some countries. Moreover, the selection of essential medicines and development of robust evidence-based guidelines can be especially difficult in re-

lation to mental disorders, as the evidence on psychotropic medicines has several methodological limitations.

Lack of a national mental health policy is another barrier: according to WHO's Mental Health Atlas 2014, only 131 countries - just 68% of WHO's Member States - reported the existence of a stand-alone policy or plan for mental health (14). A national mental health policy serves as an official statement by government or health authority on the overall direction for mental health care, defining a vision, values, principles and objectives and establishing a model of action to achieve that vision (14).

ACCESS TO MEDICINES FRAMEWORKS

An access to medicines framework was developed in 2000 during a consultative meeting between WHO and Management Sciences for Health (MSH) (15). In 2004, WHO defined four dimensions of access to medicines: rational selection, affordable prices, sustainable financing, and reliable health and supply system (7), with quality assurance and management systems assumed to underpin all access components.

In more recent years the WHO access to medicines framework has been further developed, in particular following the recognition that it should be considered within the broader context of accelerating the achievement of universal health coverage. A health systems approach situates medicines against the full complexity of a health system, showing how interventions in the pharmaceutical sector influence the rest of the health system and vice versa (16). Within this framework, access to medicines would depend on which medicines are selected for inclusion on a national essential medicines list and on whether they are available, affordable and appropriately used (16, 17).

Interventions for improving access to medicines may also be organized into four different levels of the health care system, the first three of which relate to the supply side and the last to the demand side: international; national or subnational (state or provincial); district; and individual, household or community (9). A 4 x 4 framework, as illustrated in Table 1, may be adopted to show the levels at which actions may be activated for each access component.

Following this 4 x 4 framework, the next four chapters describe the actions and initiatives that may be organized for each access component at different health-care levels to promote better access to medicines for mental disorders. Practical instructions on appropriate prescribing are then presented.

Table 1. 4x4 framework mapping the components of access across four levels of the health system

Side	Level	ACCESS COMPONENTS			
		SELECTION	AVAILABILITY	AFFORDABILITY	APPROPRIATE USE
Supply	International				
	National or subnational				
	District health service				
Demand	Individual, household or community				

PROMOTING RATIONAL SELECTION OF MEDICINES FOR MENTAL DISORDERS

Rational selection refers to the careful selection of medicines based on best available evidence to inform practice and to ensure economic viability of health-care systems. Because of its significant impact on both quality of care and cost of treatment, careful selection of medicines is considered to be one of the most cost-effective means of improving health care.

From the standpoint of both prescriber and consumer, careful selection reduces duplication and confusion while increasing the likelihood of side-effects being monitored and adverse events prevented. Prescribers, dispensers and consumers can more easily remember therapeutic effects and adverse reactions and do not have to cope with too many different dosage regimes and confusing nomenclature. Careful selection also allows for a simpler and more efficient approach to training in both prescribing and dispensing.

Rational selection facilitates bulk purchase and easier management of the storage and distribution of medicines and is considered to be a prerequisite for establishing a sustainable supply system or a sound insurance reimbursement system (13, 18). It also facilitates monitoring of the use of medication and of the quality of medicines (19). Poor selection may result in reduced availability and affordability of key medicines even when later stages of the procurement cycle are properly managed.

For mental disorders, the rational selection of medicines is particularly relevant. Many of the available psychotropic medicines are duplicative or nonessential, being minor variations of originator products with unclear therapeutic advantages, if any, over other medicines already on the market. In many cases, new medicines are released with inadequate information on comparative efficacy and tolerability, leading to uncertainty as to their effectiveness compared with other medicines already in use. Moreover, newer psychotropic medicines are considerably more expensive than older medicines.

Table 2 summarizes actions and initiatives for the careful selection of a limited number of psychotropic medicines.

DEVELOPING A MEDICINE SELECTION PROCESS (ACTION 1)

The WHO Model List of Essential Medicines

No public sector or health insurance system can afford to supply or reimburse all medicines that are available on the market. Essential medicines lists - at both international and national level - are useful in setting priorities for all aspects of the pharmaceutical system.

The WHO Model List of Essential Medicines (EML) has been updated every two years since 1977. Medicines are specified by international nonproprietary names (INN) or generic names, without reference to any brand name or specific manufacturer (20).

Table 2. Actions and initiatives for careful selection of a limited number of psychotropic medicines

Level	ACTION / INITIATIVE
International	Development and regular update of the WHO Model List of Essential Medicines (Action 1)
National or subnational	Development of a medicine selection process that includes psychotropic medicines (Action 1)
District health service	Local implementation and adaptation of national or international psychotropic medicine lists (Action 1) Promotion of information and education initiatives for professionals on the selection process (Action 2)
Community	Promotion of information and education initiatives for users on the selection process (Action 2)

The main characteristics of the WHO EML are the following (18):

- The EML does not include all effective medicines, the latest medicines or even all medicines needed in a country; rather, it helps define the minimum medicine needs for a basic health system.
- According to WHO, essential medicines are those that satisfy the priority health-care needs of the population.
- WHO recommends that essential medicines be available within functioning health systems at all times, in adequate amounts, in the appropriate doses, with assured quality and at a price the individual and the community can afford.
- Countries are not bound by the WHO Model List. The List is a model starting point - a resource for the guidance of individual countries, which can then create their own essential medicines lists, modified to reflect their health priorities and needs, as well as the level of care at which medicines should be used.
- The impact of the WHO EML has been remarkable. Conceptually, it has led to global acceptance of essential medicines as a powerful means of promoting health equity. Practically, it provides a guide for the development of national, state or provincial medicines lists and helps to promote the development of medicine policies and access initiatives (20).

Box 1. Psychotropic medicines on the WHO Model List of Essential Medicines[1]

MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS

The square box symbol (☐) is primarily intended to indicate similar clinical performance within a pharmacological class.

Medicines used in psychotic disorders

☐ chlorpromazine
☐ fluphenazine
☐ haloperidol
risperidone

Complementary list (specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed)

clozapine

Medicines used in depressive disorders

☐ amitriptyline
fluoxetine

Medicines used in bipolar disorders

carbamazepine
lithium carbonate
valproic acid (sodium valproate)

Medicines for anxiety disorders

☐ diazepam

Medicines used for obsessive compulsive disorders

clomipramine

Medicines for disorders due to psychoactive substance use

nicotine replacement therapy (NRT)

Complementary list

☐ methadone (The square box is added to include buprenorphine; the medicines should be used only within an established support programme.)

[1] The selection and use of essential medicines. Report of the WHO Expert Committee, 2015 (including the 19th WHO Model List of Essential Medicines and the 5th WHO Model List of Essential Medicines for Children. Geneva: World Health Organization; 2015 (WHO Technical Report Series, No. 994).

It should be noted that chlorpromazine, fluphenazine, haloperidol, amitriptyline, diazepam and methadone are indicated as an "example of the class for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources." Thus, in the WHO EML: amitriptyline represents tricyclic antidepressants; chlorpromazine represents phenothiazines; diazepam represents benzodiazepines; fluphenazine represents injectable long-acting antipsychotics; haloperidol represents butyrophenones; and methadone also represents buprenorphine.

Most countries have national lists and some have state or provincial lists as well. National lists of essential medicines usually relate closely to the national guidelines for clinical health-care practice, which are used for the training and supervision of health workers.

District medical officers should be aware that the concept of essential medicines is intended to be flexible and adaptable to many different situations, including private and public sectors and different levels of the health-care system (18). Many NGOs and international non-profit supply agencies have also used the concept of essential medicines. In conjunction with evidence-based clinical guidelines and other tools that may facilitate rational prescribing, a selection of essential psychotropic medicines can help in establishing rational prescribing habits (18).

Box 2. Effectiveness of the essential medicines concept in low- and middle-income countries[1]

A study was carried out to explore whether medicine use in the public sector is better in low- and middle-income countries that have implemented essential medicines policies than in those that have not.

Data were available for 56 countries. The study found a positive correlation between the number of medicine policies that countries reported implementing and the quality of their medicine use. This correlation was strongest - and statistically significant - in countries with national per capita wealth levels below the median of the study countries, underscoring the importance of essential medicines policies in low-income countries.

This study provided the strongest evidence to date that some essential medicines policies are effective.

[1] Source: reference 21.

Box 3. Usefulness of the essential medicines list as a reference tool[1]

A study was carried out to compare the recently introduced national medicines list of the Federation of Bosnia and Herzegovina with the WHO EML and other evidence-based tools.

Limited overlap was found between the two lists: of 334 medicines listed on the national medicines list of Bosnia and Herzegovina, 151 were not included in the WHO EML. For 89 (27%) of the medicines in the national list no evidence good enough to justify their inclusion was found either in Cochrane reviews or in health-technology-assessment published reports.

The results of this study suggest that greater reliance on well-established lists of essential medicines is crucial when deciding on medicine selection and reimbursement.

[1] Source: reference 22.

Box 4. Updating the National Essential Medicine List in United Republic of Tanzania[1]

A qualitative study in which data were collected by in-depth interviews and document reviews was carried out to describe the process of updating the National Essential Medicines List in the United Republic of Tanzania and to examine the criteria and the underlying evidence used in decision-making.

The study found that the list was updated by committees of experts drawn mostly from referral hospitals and from the Ministry of Health and Social Welfare.

The authors pointed out that essential medicines in the country were selected largely through an experience-based process, in contrast to the evidence-based approach that was recommended by the WHO Expert Committee on Selection and Use of Essential Medicines in 2002.

It was concluded that the health authorities in the United Republic of Tanzania should take the necessary measures to ensure that the limited health resources are allocated to proven interventions with the greatest potential to reduce the burden of disease and meet other public health goals.

[1] Source: reference 23.

Box 5. Example of national versus state-level essential medicines list[1]

A study on access to and use of psychotropic medicines was recently conducted in Bihar, India.

Bihar produces a customized state-level essential drugs list, to be used as a guideline for clinical practice and as an indicator of medication availability at government facilities. The list is updated at least every two years by a core committee of experts and government officials.

The psychotropic medicines included in the 2013-2014 update were the following: alprazolam, amitriptyline, carbamazepine, clonazepam, diazepam, fluoxetine, haloperidol, lorazepam, magnesium sulfate, midazolam, phenobarbital, phenytoin sodium, sodium valproate, trifluoperazine combined with trihexyphenidyl. Of these, alprazolam, diazepam and magnesium sulfate are for use both in primary health centres and in medical college hospitals, while the other medicines are for use in medical college hospitals only.

Interestingly, the Bihar list is an adaptation of the National List of Essential Medicines of India. For example, imipramine, olanzapine, lithium carbonate and chlorpromazine hydrochloride are included in the National List of Essential Medicines but not in Bihar's Essential Drugs List. By contrast, clonazepam and trifluoperazine combined with trihexyphenidyl are included in Bihar's essential drugs list but not in the National List of Essential Medicines.

This is an interesting example of application of the essential medicines concept at different geographical levels and at different levels of the health-care system (primary health centres versus medical college hospitals).

[1] Source: reference 24.

The process by which psychotropic medicines are selected is of critical importance. According to WHO, the treatment that is recommended and the medicines that are selected depend on many considerations, such as the pattern of prevalent diseases, treatment facilities, the training and experience of available personnel, financial resources, and genetic, demographic and environmental factors (18).

Box 6. WHO criteria for selection of essential medicines

The rules governing the process of selecting essential medicines have changed substantially over time. In 2002, in response to growing methodological concerns (25), an approach based on a more systematic assessment of the evidence base was adopted by WHO (26).

The current process is application-driven: applications to include, change or delete a medicine are drafted on the basis of a form suggested by WHO and submitted by institutions and organizations outside WHO or by WHO departments.

The Expert Committee, appointed by the Director-General of WHO, meets every two years to review applications with expert assessors and decide which medicines are added or deleted (20). WHO selection criteria include the following (18):

- Only medicines for which sound and adequate evidence of efficacy and safety in a variety of settings is available should be selected.
- Relative cost-effectiveness is a major consideration for choosing medicines within the same therapeutic category. In comparisons between medicines, the total cost of treatment – not just the unit cost of the medicine – is considered in relation to its efficacy.
- In some cases, selection may also be influenced by factors such as pharmacokinetic properties or by local considerations such as the availability of facilities for manufacture or storage.
- Each medicine selected must be available in a form in which adequate quality, including bioavailability, can be ensured; its stability under the anticipated conditions of storage and use must be determined.
- Generally speaking, essential medicines should be formulated as single compounds. Fixed-dose combination products are selected only when the combination has a proven advantage in therapeutic effect, safety and adherence or in reducing the emergence of drug resistance for example in malaria, tuberculosis and HIV/AIDS.

National lists of medicines

The concept of selecting a limited number of medicines, including psychotropic medicines, does not imply that no other medicines are available in a country. Rather, of all medicines potentially available on the world market, only some are selected and marketed for use in a specific country, and of all selected medicines a limited number may be included in essential medicines lists.

In most countries, the marketing of medicines requires prior scientific evaluation, approval and licensing by a national medicine regulatory authority. Only medicines fulfilling a predefined set of criteria, including efficacy, safety and quality, receive marketing approval; thus, of all medicines available in the world, only a selection is available in each country.

Box 7. The selection of medicines by regulatory authorities: the example of Brazil[1]

In Brazil, the process of drug selection is governed by the Brazilian National Health Surveillance Agency, ANVISA. Created in 1999, ANVISA is linked to the Ministry of Health but is financially autonomous and independently administered. Its activities involve the setting of standards and rules, together with inspection and health surveillance enforcement.

ANVISA provides instructions to pharmaceutical companies based on a legal and hierarchical framework of laws, decrees, ordinances, resolutions, normative acts and instructions. ANVISA gives priority to registration of drugs with the greatest potential impact on public health, including new generics.

ANVISA has sought to harmonize its requirements with those of larger agencies such as the European Medicines Agency and Food and Drug Administration (FDA), prioritizing what is required by WHO. However, some requirements in Brazil are region-specific.

[1] Source: www.anvisa.gov.br

Box 8. The selection of medicines by regulatory authorities: the example of European countries[1]

The European Medicines Agency (EMA) is an agency of the European Union, responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union. It began operating in 1995.

Any opinion expressed by the EMA on old or new products, relating to changes in therapeutic indications, approval, suspension or withdrawal of a product, has to be accepted by all members of the European Union.

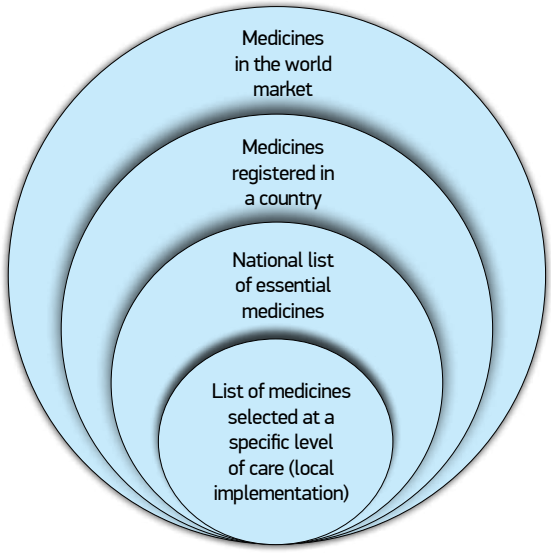
A Committee for Medicinal Products for Human Use (CHMP) is responsible for informing the EMA's opinions on all questions concerning medicines for human use, in accordance with Regulation (EC) No. 726/2004. Assessments conducted by the CHMP are based on scientific criteria and determine whether or not the medicines concerned meet the necessary quality, safety and efficacy requirements (in accordance with EU legislation, particularly Directive 2001/83/EC). These processes ensure that medicines have a positive risk-benefit balance in favour of patients/users of these products once they reach the marketplace.

[1] Source: http://www.ema.europa.eu/ema/

At local levels, there may be implementation and adaptation of lists of medicines, depending on availability of services and expertise. The natural consequence of this is that different lists of medicines, including different selections of psychotropic medicines, are usually developed for use in different health-care settings (hospitals, community health-care centres, dispensaries and any other public or private or nongovernmental facility), as illustrated in Figure 1.

It is critical to bring together all stakeholders involved in decisions about how the selection process is organized and about individual medicine inclusion in or removal from national, subnational or local lists. The WHO Department of Essential Medicines and Health Products, in collaboration with the Rational Pharmaceutical Management Plus Program of MSH, suggested that Drug and Therapeutic Committees (DTCs) may actively contribute to the selection process and implementation of appropriate prescribing of medicines, including psychotropic medicines (27). DTCs may exist at any level within the health-care system: at the national level, at the district level (overseeing primary health-care facilities) or in hospitals.

Figure 1. Selection of medicines for use at different levels of the health care system



PROMOTING INFORMATION AND EDUCATION ACTIVITIES FOR STAFF AND USERS ON THE SELECTION PROCESS (ACTION 2)

As the credibility of the selection process is likely to have a profound influence on access to psychotropic medicines, both professionals and users should be regularly provided with adequate information on how the system works, on rules governing the inclusion of new medicines and on the national and/or local officials responsible for proper functioning of the system.

Box 9. Credibility of the medicines selection process: an example from India[1]

In recent years, concerns have been expressed internationally about the selection of medicines in India, where thousands of fixed-dose combination (FDC) products are available. In 2011, in response to these concerns, an Indian standing committee closely examined the Indian national drug regulator - the Central Drugs Standard Control Organization (CDSCO). The committee released a report in 2012, highlighting multiple deficiencies in the approval processes of the CDSCO, including a failure to test the efficacy and safety of many of the FDCs available in India.

A time-trend analysis was carried out of the sales volumes of oral FDCs for pain relief (analgesia; formulations of non-steroidal anti-inflammatory drugs), diabetes (metformin formulations), depression/anxiety (antidepressant/benzodiazepine formulations), and psychosis (antipsychotic formulations) in India between 2007 and 2012. It found that large numbers of unapproved formulations are available for three of the four therapeutic areas examined, and that sales volumes of these unapproved FDCs (some of which contained internationally banned or restricted drugs) are high.

The researchers make several recommendations to remedy this situation. Sale and manufacture of unapproved FDC formulations, they suggest, should be banned immediately. Withdrawal from the market should be staged, with priority given to removing those formulations containing medicines that are banned or restricted internationally. To ensure in the long-term the safety and effectiveness of new medicines marketed in India, as well as transparency of the approval process, the researchers call for amendments in India's regulatory processes and drug laws.

[1] Source: reference 28.

The medicine selection process should be consultative and transparent, with publicly available and explicit selection criteria. Applications should be accessible to both professionals and the public, with reasons for acceptance or rejection of a new medicine reported on a dedicated website. Feedback from professionals, including policy-makers, prescribers, nurses and all others involved in the provision of medicines, as well as from end-users and the wider public, should be routinely collected and used to inform and improve the selection process. This approach may be applied to any level within the health-care system at which a selection process is operating: at district level (overseeing primary health-care facilities), in hospitals, or at subnational (state or provincial) or national level.

IMPROVING AVAILABILITY OF QUALITY MEDICINES FOR MENTAL DISORDERS

Availability in this context pertains to the timely obtainability of quality medicines in the public and private sector. Despite recent progress, availability of medicines for mental disorders remains a major challenge globally: it is estimated that essential medicines are unavailable or available only irregularly for up to one third of people in the developing world (7, 8).

- In 2009, the WHO-AIMS study of mental health systems found that only 14% of African countries had at least one psychotropic medicine available in all public health facilities (29).
- In Nigeria, even after a 15-year programme focusing on the scale-up of mental health-care treatment in primary care settings, essential psychotropic medicines were not routinely available to the majority of public health facilities (30).
- A recent study in Sofala, Mozambique, found that essential psychotropic medicines are routinely unavailable at public health facilities. Only 7 of 12 district warehouses and 11 of all 24 health facilities (and 10 of 12 health facilities with trained staff) had access to at least one medicine in each category (31).
- Disruption of usual supply chains in humanitarian emergencies - arising from armed conflicts or natural or industrial disasters - may seriously limit the availability of medicines for mental disorders (32).

Availability of quality psychotropic medicines depends upon a number of factors, both distal and proximal to the end user (33). At subnational and national levels, availability is determined by processes for medicine regulation and functional supply systems, including procurement and distribution chains. At district and community levels, availability of quality psychotropic medicines is affected by the reliability of health systems and structures, especially in remote and rural areas where the density of providers may be very low. Lastly, perceptions and acceptability of mental health treatment within communities can affect availability.

Table 3 summarizes actions and initiatives for increasing the availability of medicines for mental disorders.

Table 3. Actions and initiatives for increasing the availability of medicines for mental disorders

Level	ACTION / INITIATIVE
International	
National or subnational	Regulating psychotropic medicine availability (Action 3) Implementing a reliable supply system (procurement, supply, distribution) (Action 4) Ensuring quality of psychotropic medicines (Action 5) Developing a community-based system of mental health care (Action 6)
District health service	Implementation of strategies to provide mental health care in remote and rural areas and ensure distribution of medicines at this level (Action 6)
Community	Promotion of initiatives on the acceptability of mental health care including medicines for mental disorders (individuals' perceptions, attitude and expectations to be appropriate) (Action 6)

REGULATING PSYCHOTROPIC MEDICINE AVAILABILITY (ACTION 3)

In addition to the selection of medicines, a national medicine regulatory authority should develop and implement legislation and regulations on pharmaceuticals, to ensure the quality, safety and efficacy of medicines as well as the accuracy of product information (19, 34).

As part of these licensing activities, the national authority is also responsible for implementing measures that may affect the availability of medicines at different levels of the health-care system. Some of these measures may be particularly relevant for psychotropic medicines and require potentially difficult decisions on the following:

- **Whether doctors alone or also other professionals can prescribe psychotropic medicines, including initial and subsequent prescriptions.** For example, in Ghana, South Africa and some parts of East Africa, nurses and other specific (non-doctor) medical professionals are legally able to prescribe. The legal sanction to prescribe is often limited to specific defined medicines, sometimes in specific circumstances or programmes (35). In most of Africa, however, nurses prescribe in a semi-official way, even when there is no legal provision for this. In many projects, as reported by Eaton (35), psychiatric nurses prescribe where they are part of a programme team and have adequate training and supervision; this seems to be an emerging standard in the area. To balance the need for availability with safety and appropriateness of prescribing, decisions about which medicines should be made available "over-the-counter" to consumers and which should be available only on prescription are also important. Regulations may be used to allow trained paramedical workers such as nurses - and, in some cases, village health workers - to prescribe certain types of medicines (13).
- **Availability in public and private sectors and level of the health system at which medicines for mental disorders may be accessed.** For example, the WHO mhGAP Intervention Guide underlines that it is a widely shared but mistaken idea that all mental health interventions are sophisticated and can be delivered only by highly specialized staff, while research in recent years has demonstrated the feasibility of delivery of pharmacological and psychosocial interventions in non-specialized health-care settings (36). A national medicine regulatory authority should establish the level of the health care system at which a medicine may be prescribed and the conditions under which this may be done; relevant considerations are efficacy, safety, adverse effects, costs and feasibility issues. In several low-income settings, medicines are offered only in selected secondary and tertiary health facilities, which implies diminished availability.
- **Whether medicines for mental disorders should be labelled for use in individuals with specific diagnoses.** This may mean that a formal diagnosis should be made before treatment is prescribed, and that not all individuals may receive the medicine in question. In most countries, for example, clozapine is labelled for use only in individuals with treatment-resistant schizophrenia.

Box 10. Access to clozapine according to the WHO mhGAP Intervention Guide[1]

According to the WHO mhGAP Intervention Guide, clozapine may be considered by non-specialist health-care providers, preferably under the supervision of mental health professionals, for the treatment of individuals who have not responded to other antipsychotic agents at adequate dosages for adequate duration.

Clozapine should be considered only if routine laboratory monitoring is available, because of the risk of life-threatening agranulocytosis.

[1] Source: reference 36.

- **Whether some medicines for mental disorders should be subject to regulations relating to controlled medicines**. As there is a mistaken view that all medicines for mental disorders are potentially drugs of abuse, it should be extremely clear which medicines require storage in double-locked cupboards, signatures in a register to record movement, and labelling as specialist drugs, which means that primary health-care workers cannot prescribe them.

An effective medicine regulation system is a key component of any access initiative, aiming to regulate clearly which medicines should be available at each level of the health-care system and who can prescribe them, for which clinical conditions and in what circumstances.

IMPLEMENTING A RELIABLE SUPPLY MANAGEMENT SYSTEM (ACTION 4)

A functioning and reliable supply system is needed to translate into practice what national regulatory authorities advise. As reported by WHO, designing an efficient system for procuring, storing and distributing medicines is both challenging and critical if effective supplies are to be ensured. Skills in operational planning are needed for developing a cost-effective distribution system, and it is important to have a well-qualified procurement and supply management team (13), designed in accordance with the national medicine policy. An effective supply chain that delivers these medicines to the end users affordably, reliably, robustly and in an equitable manner is especially relevant in improving access to medicines for mental disorders.

According to WHO, an effective medicines supply system depends on an appropriate mix of public, private and NGO procurement, storage and distribution services (7). The roles of government and of the private sector, however, will vary widely, depending on the organization of the health-care system. For medicines for mental disorders, the supply chain (procurement, storage, distribution of the product from point of production to point of consumption) is particularly challenging as maintaining high quality and product integrity, and minimizing diversion or misuse, requires efficient health-care systems. Effective supply chains could result in better forecasting of need and reduced stock-outs or over-stocking of medicines.

Box 11. Types of medicine supply strategies[1]

- Central medical stores: centralized, fully public management, warehousing and delivery system.
- (Semi-)autonomous supply agency: centralized, (semi-)private management and warehousing system.
- Direct delivery system: centralized decision-making but decentralized, private direct-delivery system.
- Prime distributor: centralized decision-making but decentralized, private warehousing and delivery system.
- Fully private supply: decentralized decision-making, fully private wholesalers and pharmacies system.

[1] Source: reference 7.

Box 12. Medicine supply strategy during large-scale emergencies[1]

In response to large-scale emergencies, United Nations agencies and international and nongovernmental organizations are increasingly called upon to prevent and manage serious threats to the survival and health of the affected populations. Medicines and medical devices have been supplied by relief agencies for decades.

In the 1980s, WHO facilitated a process to encourage the standardization of medicines and medical devices needed in emergencies in order to permit efficient and effective responses. This initial work led to the supply of standard, prepacked kits that could be kept in readiness to meet priority health needs in emergencies. The concept of the emergency health kit has been adopted by many organizations and national authorities as a reliable, standardized, affordable and rapidly available source of the essential medicines and medical devices urgently needed in a disaster situation.

The Interagency Emergency Health Kit (IEHK), now in its fourth edition, is a large box containing medicines and medical supplies designed to meet the expected primary health-care needs of 10 000 people exposed to major humanitarian emergencies for up to 3 months. The IEHK ensures availability of the following psychotropic medicines:

- amitriptyline tablets: 25 mg x 4000
- biperiden tablets: 2 mg x 400
- diazepam tablets: 5 mg x 240
- diazepam injections: 5 mg/ml, 2 ml/ampoule x 200
- haloperidol tablets: 5 mg x 1300
- haloperidol injections: 5 mg/ml, 1 ml/ampoule x 20
- phenobarbital tablets: 50 mg x 1000.

[1] Source: reference 32, 37.

The following actions should be implemented to address ineffective supply chains (10), although there is no globally applicable "one-size-fits-all" solution and the need for country-specific solutions is widely acknowledged:

- development of an information network systems approach for improved communication between the various tiers of the supply chain, leading to streamlined and continuous flow of data;
- training in data collection and analysis, to improve forecasting and reduce stock-outs and over-stocking;
- integrating information systems of other vertical supply chain programmes;
- increased training of supply chain staff on logistic management information systems and of all levels of health-care providers about supply chains and logistics;
- increased allocation of human resources for supply chains and inclusion of supply chain workers in determining needs for health-care systems;
- use of mobile technology across tiers of the supply chain and/or facilities;
- establishment of therapeutic committees at health institutions to conduct coordination efforts and consider information on needs, stocks and supply chain management;
- reduction in the number of tiers between central warehouses and patient distribution points;
- improved transportation between central warehouses and local distribution points to reduce the time and costs involved in delivering medicines;
- increased working capital funds for national medicine supply agencies.

Box 13. Availability of essential medicines in Pakistan[1]

In order to expand knowledge on access to essential medicines in Pakistan, exploratory research was carried out using key informant interviews with policy-makers, providers, industry, NGOs, experts and other stakeholders.

The study found weaknesses in medicine registration (excessive registration of medicines) and quality assurance systems, unclear pricing schemes and counterproductive pricing policies, and overall sub-optimal medicine availability.

[1] Source: reference 38.

ENSURING QUALITY OF PSYCHOTROPIC MEDICINES (ACTION 5)

The concept of quality refers to the need for medicines reaching patients to be safe, effective and of acceptable quality. Although international standards for the quality of medicines are becoming stricter, actual quality on the market in many countries has become a cause for major concern. Up to 15% of all medicines sold may be of inadequate quality, and in parts of Africa and Asia this figure exceeds 50% (39). The term poor-quality medicines includes counterfeit, substandard and degraded medicines as well as medicines that fail chemical analysis but for which there is insufficient information to determine whether they are counterfeit, substandard or degraded (40).

Box 14. Counterfeit medicines in Nigeria[1]

Counterfeit drug preparations in Nigeria included those without active ingredients, toxic preparations, expired drugs that were relabelled, drugs issued without complete manufacturer information, and drugs that were not registered with the National Agency for Food and Drug Administration and Control (NAFDAC).

[1] Source: reference 41.

Ensuring quality medicines in a country starts at the central level. Challenges involved in the regulation of medicines include licensing and inspection of sales points and of health-care professionals, licensing and inspection of manufacturers, registration of medicines, implementing good distribution and storage practices (GDP, GSP), and post-marketing surveillance.

Quality must also be guaranteed throughout the distribution chain, in all climates and by all methods of transportation. National regulatory authorities should ensure that the following activities are regularly conducted (34):

- licensing of the manufacture, import, export, distribution, promotion and advertising of medicines;
- assessment of safety, efficacy and quality of medicines, and issue of marketing authorization;
- inspection and surveillance of manufacturers, importers, wholesalers and dispensers of medicines;
- ensuring implementation of GDP and GSP, as well as guidance from the Model quality assurance system for procurement agencies (34, 42, 43);

- controlling and monitoring the quality of medicines on the market;
- controlling promotion and advertising of medicines;
- monitoring adverse reactions to medicines;
- providing independent information on medicines to health professionals and the public.

Box 15. Quality of essential medicines in Pakistan[1]

In the study of the availability of essential medicines in Pakistan, it was found that only 35% of domestic demand is met by local manufacturing units, and raw material for local medicine production is almost entirely imported.

Market surveillance conducted by the provincial Departments of Health involves sampling of drugs on the market but there continues to be a high proportion of counterfeit drugs.

[1] Source: reference 38.

Box 16. Sourcing of medicines in sub-Saharan Africa[1]

A review article by Eaton describes some of the problems associated with providing medicines in health services in sub-Saharan Africa and reports that medicines are procured by a variety of routes.

Government services are usually able to access medicines through formal channels or have a pharmacy department experienced in procurement. Smaller projects or hospitals may have to rely on less regular routes.

Procurement is easiest through the private market, when it is the dealer who sources the medicines. However, medicines bought in this way may be expensive, and there is little opportunity to vet the original sources. At the other extreme, it is possible to import medicines directly from agencies in industrialized countries, particularly those that specialize in supplying to the developing world. A source that is helpful for some nongovernmental projects is the agencies that specifically supply mission hospitals and charitable organizations. Many large international NGOs have experience of importing their own medicines, often using an agreed standard list. However, it is generally agreed that procurement through local established sources is preferable, strengthens local systems and is more sustainable.

[1] Source: reference 35.

Box 17. Nigerian experience with counterfeit and substandard drugs[1]

In 2005 the Nigerian National Agency for Food and Drug Administration and Control (NAFDAC) resolved that counterfeit medicines had to be minimized in the shortest possible time. The Agency implemented the following actions to eradicate fake medicines and other substandard regulated products:

- staff reorientation and motivation;
- restructuring and modernization of regulatory processes;
- public awareness campaigns;
- stopping the importation of fake drugs to Nigeria at source;
- strengthening of surveillance at all ports of entry;
- "mopping up" what was already in circulation;
- regular monitoring of good manufacturing practice of local manufacturers;
- streamlining and strict enforcement of registration guidelines.

Thanks to these actions, the number of fake medicines was reduced by more than 80%, and a culture of transparency and accountability was progressively implemented.

[1] Source: reference 44.

Box 18. The WHO Model quality assurance system for procurement agencies

The WHO Model quality assurance system for procurement agencies (MQAS)[1] is a guidance document developed at the request of the Global Fund to Fight AIDS, Tuberculosis and Malaria and adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations in 2006.

In the years that followed, international organizations involved in medicines procurement incorporated the MQAS requirements into their quality assurance policies and phased in stringent, harmonized quality criteria for key product categories procured in large quantities and considered crucial for the success of treatment programmes.

[1]MQAS: http://www.who.int/medicines/areas/quality_safety/quality_assurance/TRS986annex3.pdf?ua=1
Assessment tool: http://www.who.int/medicines/areas/quality_safety/quality_assurance/TRS986annex4.pdf?ua=1

DEVELOPING A COMMUNITY-BASED SYSTEM OF MENTAL HEALTH CARE (ACTION 6)

Community- and general hospital-based care

The geographical location of health services may significantly reduce the availability of care, including mental health care and the availability of medicines for mental disorders. The mhGAP initiative underlines the feasibility of delivery of interventions, including medicines for mental disorders, in non-specialized health-care settings. Health-care providers in these settings may be working in a health centre or as part of the clinical team at a district-level hospital or clinic. They include general or family physicians, nurses and clinical officers. Non-specialist health-care providers can use the mhGAP-Intervention Guide with appropriate adaptation.

According to this model, primary health care is considered the foundation for high-quality mental health care. Where mental health is integrated into primary care, access is improved, mental disorders are more likely to be identified and treated, and comorbid physical and mental health problems are managed in a seamless way (17).

A balanced care model would suggest that a comprehensive mental health system should include both community- and hospital-based care (psychiatric wards in general hospitals). However, given the huge variations in resources available at national and local levels, the balanced care model should be adapted locally (45). In order to maximize access to mental health care in LMICs, it could include the following (45):

- Primary care mental health:
  - case-finding and assessment
  - talking and psychosocial treatment
  - pharmacological treatments.
- Limited provision of some services by specialist staff:
  - training and supervision of primary care staff
  - consultation–liaison for complex cases
  - outpatient and inpatient assessment
  - treatment for cases that cannot be managed in primary care.

Outreach interventions

Strategies to increase access to treatment for people with more disabling mental disorders are based on the assertive community treatment model (45; 46) or on similar approaches, characterized by the following features:

- small case-loads (a team of about 10 core staff members assigned to about 100 patients);
- continuous services (operating 24 hours a day, 7 days a week);
- medication delivered by team members daily if necessary;
- potential for patients to graduate to less intensive interventions;

- a team approach, drawing on the contributions of psychiatrists, nurses and other health professionals;
- patient finances arranged or directly managed by the team;
- a target of 80% of team activity taking place in the community.

It should be noted, however, that the extent to which these models are relevant and appropriate for use in LMICs has yet to be established (46). Nevertheless, they represent an interesting example of the possibility of developing ad hoc outreach initiatives that may significantly increase access to mental health care, including access to medicines for mental disorders.

Box 19. A telepsychiatry model to support psychiatric outreach in the public sector in South Africa[1]

Telepsychiatry is the practice of psychiatry over distance using information and communication technologies. In KwaZulu-Natal, South Africa, a telepsychiatry outreach model was developed on the basis of local research and international evidence. The model aimed to provide specialist psychiatry services that were unavailable at local health services through video conferencing instead of face-to-face consultation.

Implementation of the model achieved the following results:

- improved access for mental health-care users at local hospitals to specialist psychiatric services, with a resultant reduction in unplanned transfers to psychiatric hospitals;
- increased contact through supervision and continuing education between local health staff without post-qualification psychiatry training and psychiatry specialists, resulting in decreased isolation and increased mental health skills and competencies;
- reductions in the time and cost of outreach travel for consultant psychiatrists.

[1]Source: reference 47.

Box 20. On-site mental health services in Philadelphia, USA[1]

A study conducted in Philadelphia examined whether on-site mental health services, provided in an inner-city adolescent medicine clinic, would improve the rate of patients first meeting with a mental health-care provider compared with patients referred to off-site providers through their insurance companies. Only one (2.6%) of the 38 participants referred off-site ever received counselling. Of the 33 participants referred on-site, 22 (66%) received counselling.

Despite the small sample of individuals recruited, this study showed that, while many obstacles impede the access of low-income, inner-city adolescents to mental health services through the traditional route of medical assistance insurance, many of these obstacles can be at least partially overcome by placing a counsellor within the primary care site.

[1]Source: reference 48.

Initiatives on the acceptability of mental health care

On the demand side, poor help-seeking behaviour is a key barrier in relation to access to treatment, reducing demand for medicines for mental disorders (11, 12). Even when services providing mental health care are available, individuals may not seek care because of poor knowledge about and persistent stigma associated with mental disorders. A study carried out in three states in the Yoruba-speaking parts of Nigeria, for example, found that more than 40% of household respondents believed some mental disorders to have supernatural causes and 30% believed in faith or spiritual treatments rather than medical treatments (49). The negative attitudes of others may also discourage people with mental disorders from seeking treatment – for many, there is perceived shame associated with mental illness.

During a recent workshop on access to essential medicines for mental, neurological and substance use disorders in sub-Saharan Africa (10), the following suggestions for improving access through increased demand were made:

- improve help-seeking through public education;
- enhance detection and treatment of mental disorders through provider training designed to improve skills and reduce negative attitudes;
- reform the health system so that the few specialists available can spend more time providing supervision and support to first-line providers;
- engage policy-makers to improve procurement.

Workshop participants argued that implementation of the mhGAP Intervention Guide and training modules might be a strong first step in addressing the need for increased and improved training and education of providers and managers (38).

Box 21. mhGAP example of enhanced detection and treatment of mental disorders in Ethiopia[1]

In Ethiopia, the Federal Ministry of Health issued a Mental Health Strategy for the development of mental health services that are "decentralized and integrated at the primary health-care level". A system for implementing the WHO mhGAP was developed to address the basic needs of people with mental disorders. It was particularly successful in terms of:

- training non-mental health professionals to deliver care for people with mental, neurological and substance use disorders according to the training package of the mhGAP Intervention Guide;
- engaging mental health professionals in training, supportive supervision and mentoring;
- increasing the involvement of Regional Health Bureaux;
- developing a data quality framework on relevant indicators;
- ensuring that essential psychotropic medicines are continuously available at health-facility level.

[1]Source: reference 50.

Box 22. Review on the nature and impact of demand-side interventions[1]

The following interventions have been suggested as reducing demand-side barriers, as reported in the international literature:

- Lack of knowledge:
  - staff conduct outreach activities to provide services;
  - communities given information on when to seek care and on range of providers.
- Low ability to assimilate health choices:
  - improve access to primary education;
  - stimulate demand using financial incentives to seek treatment.
- Reluctance to seek health care for women outside home:
  - information and education;
  - culturally-sensitive health-care delivery.
- Patients seeking care from providers inappropriate for their condition;
  - information and education.

[1]Source: reference 51.

IMPROVING AFFORDABILITY OF MEDICINES FOR MENTAL DISORDERS

As many mental disorders require long-term regular pharmacological treatment, the cost of medicines may constitute a relevant barrier to access and appropriate use. In many low-income countries, little is known about the affordability of medicines for treating mental disorders. With poor availability of medicines in the public sector, individuals are often forced to look to the private sector where prices may be prohibitive (10).

Affordable prices for essential psychotropic medicines are important in both public and private sectors. New medicines are often very costly and pricing cannot be left solely to market forces: active government involvement and intervention are required (13).

Table 4 summarizes actions and initiatives for increasing the affordability of medicines for mental disorders.

Table 4. Actions and initiatives for increasing the affordability of medicines for mental disorders

Level	ACTION / INITIATIVE
International	Developing policies on affordability of medicines (Action 7)
National or subnational	Developing pricing policies and fostering a sustainable financing system with affordable medicine prices (Action 8)
District health service	
Community	

DEVELOPING POLICIES ON AFFORDABILITY OF MEDICINES (ACTION 7)

Although psychotropic medicines on the WHO Model List are off-patent and therefore available at low cost from many producers, newer medicines that may be added to the Model List in future may be prohibitively expensive as a result of patent protections.

In 2001, LMICs, concerned that developed countries were insisting on an excessively narrow reading of the international agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS)[1], initiated a round of talks that culminated in the Doha Declaration on the TRIPS Agreement and Public Health. As reported by WHO, the Declaration states that the World Trade Organization and its Member States:

- Recognize the gravity of the public health problems afflicting many developing and least-developed countries, especially those resulting from HIV/AIDS, tuberculosis, malaria and other epidemics.
- Stress the need for the TRIPS Agreement to be part of the wider national and international action

[1] *The TRIPS Agreement has been in force since 1995 and is to date the most comprehensive multilateral agreement on intellectual property.*

to address these problems.

- Recognize that intellectual property protection is important for the development of new medicines, but are also concerned about its effect on prices.
- Agree that the TRIPS Agreement does not and should not prevent Members from taking measures to protect public health. Accordingly, while reiterating the commitment to the TRIPS Agreement, it is affirmed that the Agreement can and should be interpreted and implemented in a manner supportive of WTO Members' rights to protect public health and, in particular, to promote access to medicines for all.

A further development of TRIPS is "TRIPS-plus", which refers to efforts to: extend patent life beyond the 20-year TRIPS minimum; limit compulsory licensing in ways not required by TRIPS; and limit exceptions which facilitate a prompt introduction of generics (13). Countries are advised to be cautious about enacting legislation that is more stringent than the original TRIPS requirements.

DEVELOPING PRICING POLICIES AND FOSTERING A SUSTAINABLE FINANCING SYSTEM AND AFFORDABLE PRICES (ACTION 8)

Most LMICs rely on a diverse set of health and drug financing mechanisms which can help cover the cost of medicines. According to WHO, the following aspects should be considered for both better and greater public spending on health and essential medicines (7):

- increased public funding for health and medicines.
- cost sharing with patients, as a transitional measure towards long-term aims, such as universal health insurance.
- donor funding for, and donations of, medicines can have an impact on health progress in LMICs in the short term; in the medium term these donations should be targeted at specific diseases and planned as additional supplies, integrated into the national medicine supply system, but in the long term, self-sufficiency is the only viable means to tackle increasing disease burdens.

During a recent workshop on access to essential medicines for mental, neurological and substance use disorders in sub-Saharan Africa (10), the following suggestions for improving psychotropic medicine affordability were made :

- promote and prioritize low-cost generics;
- reduce or remove tariffs, taxes and mark-ups;
- establish reference prices for reimbursement;
- include essential medicines for mental disorders in reimbursement/insurance schemes and international financing mechanisms;
- reduce charges or co-payments, with a focus on generics.

Affordable prices can be pursued through the following mechanisms, which have been explained elsewhere (7):

- Price information - helps in price negotiations, in locating new supply sources and in assessing the

efficiency of local procurement.

- Price competition, through tendering of generic products, and therapeutic competition - are powerful price-reduction tools.
- Bulk procurement - medicine orders are pooled together, the focus is on a list of priority medicines and duplication within therapeutic categories is avoided as far as possible.
- Generics policies - are effective instruments when a patent expires.
- Equitable pricing - is especially important for newer essential medicines that are still protected by patents or other instruments that provide market exclusivity. Equitable pricing is explained as the adaptation of prices that are charged by the manufacturer or seller to countries with different purchasing power.
- Reduction or elimination of duties and taxes for both generic and patented essential medicines - contributes to price reduction.

Several countries have adopted policies that encourage generic prescription and dispensing. Large generic medicine markets have started to develop in some countries (especially the USA and in Europe). Promotion of the use of generic medicines in the private sector is difficult because of inadequate information for health professionals and the failure to provide financial incentives at sales points. Competitive bulk procurement by generic name is now a major policy in most essential medicines programmes and in large hospitals in both developed and developing countries.

It is important to include mental health treatment and medicines in benefit packages under reimbursement systems in countries where such systems exist. A specific evidence-based guideline on country pharmaceutical policies has recently been developed by WHO together with an international panel of experts (52).

PROMOTING APPROPRIATE USE OF MEDICINES FOR MENTAL DISORDERS

The concept of appropriate use of medicines refers to the expectation that individuals receive medicines that are appropriate to their clinical needs, in doses that meet their individual requirements, for an adequate period of time, and at the lowest cost to them and their community (7, 8). Irrational use of medicines – including misuse, underuse and overuse – clearly has a negative impact on health outcomes. It can also result in a huge waste of resources.

Irrational use of medicines is a major problem worldwide. More than 50% of all medicines are prescribed, dispensed or sold inappropriately, and half of all patients fail to take them correctly. Examples of irrational use of psychotropics include prescribing or dispensing too many medicines per patient (polypharmacy), prescribing inappropriate dosages, poor adherence to correctly prescribed medications, as well as misuse, underuse or overuse.

Box 23. Antipsychotic drug use in patients with schizophrenia discharged from psychiatric units in Poland[1]

A survey carried out in Poland investigated the prevalence of polypharmacy in 207 patients with schizophrenia whose clinical status was stable at discharge from psychiatric wards. It found that 109 (52.7%) of the patients were prescribed one antipsychotic drug, 88 (42.5%) two antipsychotics and 10 (4.8%) three antipsychotics. The third was usually a low-potency agent (chlorprothixene, levomepromazine) prescribed for reported insomnia. The frequency of polypharmacy in the six hospitals surveyed ranged from 38% to 52%. In addition to antipsychotics, mood stabilizers were prescribed for nearly one third of the patients, while antidepressants and benzodiazepines were prescribed for fewer than 10%.

These findings highlighted the need to investigate why antipsychotic polypharmacy is considered a treatment option for some patients and the short- and long-term beneficial and harmful consequences of this practice.

[1]Source: reference 53.

Box 24. Prescribing trends of benzodiazepines in the Republic of Korea[1]

A survey carried out in the Republic of Korea looked at benzodiazepine prescribing trends for adults between 2007 and 2011. The average national benzodiazepine prescription prevalence for 1 year was: 23.7% for one day's supply or more; 7.9% for 30 days' supply or more; 4.7% for 90 days' supply or more; and 3.2% for 180 days' supply or more.

The authors suggested that benzodiazepines were being prescribed inappropriately and that the policy of limiting continuous prescription to 30 days did not seem to be effective.

[1]Source: reference 54.

Box 25. Prevalence of psychotropic drug use among people with and without Alzheimer disease in Finland[1]

A survey conducted in Finland investigated the prevalence of psychotropic drug use in the year following a diagnosis of Alzheimer disease. The study included 69 080 community-dwelling people with a new diagnosis of Alzheimer disease over the period 2005–2011.

During the year following diagnosis, 53% of people with Alzheimer disease purchased at least one psychotropic drug: antipsychotics were used by 20%, antidepressants by 28% and benzodiazepines by 29%. At least two psychotropic drugs were purchased by 20% of people with Alzheimer disease.

Compared with people without the disease, those with Alzheimer disease were six times more likely to use antipsychotics and three times more likely to use antidepressants; benzodiazepine use was comparable in the two groups.

This study highlighted that, despite safety warnings concerning use of antipsychotic drugs by this patient population, antipsychotic use among people in Finland with newly diagnosed Alzheimer disease increased between 2005 and 2011.

[1]Source: reference 55.

According to WHO, countering irrational use of psychotropic medicines requires action on a number of fronts. Table 5 summarizes actions and initiatives for promoting more appropriate use of psychotropic medicines.

Table 5. Actions and initiatives for promoting more appropriate use of psychotropic medicines

Level	ACTION / INITIATIVE
International	Adopting evidence-based guidelines (Action 9)
National or subnational	National adaptation of international evidence-based guidelines or development of national evidence-based guidelines (Action 9) Monitoring of use of psychotropic medicines (Action 10) Inclusion in undergraduate curricula of critical appraisal of scientific evidence and training in appropriate prescribing (Action 11)
District health service	Local implementation and adaptation of evidence-based guidelines (Action 9). Monitoring of use of psychotropic medicines (Action 10) Promotion of education and training initiatives on critical appraisal of scientific evidence and appropriate use of psychotropic medicines (Action 11)
Community	Public education about the role and limits of psychotropic medicines (Action 11)

ADOPTING EVIDENCE-BASED GUIDELINES (ACTION 9)

Evidence-based treatment guidelines, developed or adapted in conjunction with a list of essential medicines, are a crucial component of interventions for promoting appropriate use of psychotropic medicines. Clinical guidelines, often referred to as standard treatment guidelines (STGs), are systematically developed to help prescribers make decisions about appropriate treatments for specific clinical conditions.

Developing evidence-based guidelines

Given that access to and use of research findings may not be straightforward for most health-care professionals globally, it is critically important to enhance evidence-based practice. New methodologies for aggregating, synthesising and grading the quality of evidence extracted from systematic reviews have been developed over recent years, and approaches for creating evidence-based guidelines based on explicit assessments of the evidence base are now commonly employed in several fields of medicine, including mental health care. One of the most well-developed approaches is the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (56-58).

Box 26. Main features of the GRADE methodology[1]

GRADE is an approach for creating clinical practice guidelines based on an explicit assessment of the evidence base. It is suitable for:

- summarizing the evidence extracted from systematic reviews and meta-analyses into "summary of findings" tables;
- grading the quality of evidence summarized in summary of findings tables;
- grading the strength of treatment recommendations.

GRADE separates the judgement on quality of evidence from strength of recommendations.

An application called GRADE Profiler (GRADEpro) has been developed to summarize the evidence and grade its quality; it can be freely downloaded at: http://tech.cochrane.org/revman/gradepro.

[1]See http://www.gradeworkinggroup.org/index.htm for additional information on GRADE methodology and on the GRADE working group.

Notably, GRADE methodology can be employed to develop treatment recommendations at different levels of the health system, including international, national, district and local level. National efforts should be focused on developing the capacity of a pool of trainers. District health officers may then adapt existing international or national guidelines to fit local needs and medicine availability. Training materials on rational use are available at: http://archives.who.int/PRDUC2004/RDUCD/RDUCD.htm.

Box 27. Example of evidence-based guidelines developed at an international level: WHO recommendations for mental, neurological and substance use disorders

WHO's mental health Gap Action Programme (mhGAP) aims to scale up mental health services, especially in LMICs. An essential component of the Programme was the development of a model intervention guide for mental, neurological and substance use disorders identified as conditions of high priority for LMICs. Recommendations (i.e. guidelines) on interventions for the management of such high-priority conditions have been developed following the GRADE approach and form the basis of the mhGAP Intervention Guide. Interventions are for use by different health-care providers, including doctors, nurses and health workers.

WHO recommendations can be accessed at:
http://www.who.int/mental_health/mhgap/evidence/en/

WHO Intervention Guide can be accessed at:
http://www.who.int/mental_health/mhgap/en/

Box 28. Example of evidence-based guidelines developed at a national level

In the United Kingdom, the National Institute for Health and Care Excellence (NICE) provides national guidance and advice for improving health and social care. NICE was originally established in 1999 as the National Institute for Clinical Excellence, a special health authority, to reduce variation in the availability and quality of treatments and care within the national health service. In April 2013, NICE become a Non-Departmental Public Body (NDPB) accountable to the Department of Health.

NICE guidelines make evidence-based recommendations on a wide range of topics, including the prevention and management of mental health and behavioural conditions. It develops quality standards and performance metrics for those providing and commissioning health, public health and social care services; it also provides a range of informational services for commissioners, practitioners and managers across the spectrum of health and social care.

NICE guidelines can be accessed at: https://www.nice.org.uk/guidance.

Box 29. Example of evidence-based guidelines developed at a local level: Verona, Italy[1]

A project to develop guidelines on the rational use of psychotropic medicines in a catchment area of 450 000 inhabitants was carried out in Verona, Italy, using the GRADE framework. At the beginning of 2012, a selected number of mental health professionals were identified and appointed as members of a Guideline Development Group (GDG).

On the basis of efficacy, acceptability, tolerability and safety data – taking into account the risk of bias and confidence in estimates, and also taking into consideration preferences, values and practical aspects in favour of and against each intervention under scrutiny – draft recommendations were formulated and agreed by GDG members. Recommendations were submitted for consideration to all prescribers in the local catchment area, discussed in two open plenary sessions, and finally approved and disseminated for use in clinical practice.

This experience suggests that, in the absence of financial or other conflicts of interest, professionals and other stakeholders may effectively organize themselves, becoming proactively involved in the production of clinical practice recommendations that adhere to internationally accepted quality standards.

[1]Source: reference 59.

Implementing evidence-based guidelines

Once a new set of recommendations has been developed, or existing guidelines have been adopted at a health system level, these should be implemented. Implementing evidence-based guidelines may be challenging: evidence on how guidelines should be implemented to maximize benefits at sustainable cost is limited. Nevertheless, the following aspects have been shown to be relevant to optimizing implementation.

- First, if international or national treatment recommendations are adopted, local implementation should take into account issues such as value judgments, resource use, local context characteristics and feasibility, all of which may differ widely in different health-care settings.
- Second - and relevant for effective implementation - health-care professionals should be advised that guidelines should not solely dictate decisions taken with individual patients. Clinical reasoning on psychopathology and clinical phenomenology (60), careful assessment of patients' needs and expectations, and the past experience of the clinical team have all been highlighted as key features of any clinical decision process.

- Third, audit of clinical activities and feedback to health-care professionals are considered to be relevant components of any guideline implementation strategies. Prescription audit and feedback consists of analysing prescription appropriateness and then giving feedback; prescribers may be told how their prescribing compares with accepted guidelines or with that of their peers. Peer review - involving peers in audit and feedback - may be particularly effective.
- Fourth, considering that current knowledge on how guidelines should be implemented is still very limited, guideline implementation programmes should always be described and documented, in order to increase understanding of how available evidence may best be used to improve practice. If feasible, the impact of implementation programmes should be studied using reliable study designs, including randomized trials and cluster randomized trials.

Box 30. Efficacy of guideline implementation strategies[1]

A recent Cochrane review summarized the available experimental evidence on the efficacy of guideline implementation strategies in improving process outcomes (performance of health-care providers) and patient outcomes in mental health care.

Only five randomized trials were included. Although single studies provided initial evidence that implementation of treatment guidelines may achieve small changes in mental health practice, this review highlighted a gap in knowledge, with scant information available for people with mental health problems, health professionals and policy-makers.

The review called for more large-scale, well-designed and well-conducted studies to fill this gap.

These findings are in line with those of a landmark systematic review of implementation studies carried out in a wide range of health-care settings, which highlighted the paucity of data to support decisions about the guideline implementation strategies that are likely to be effective, and the need to carefully consider the limited resources usually available to health-care systems for these activities.

[1]Sources: references 61, 62

MONITORING THE USE OF PSYCHOTROPIC MEDICINES (ACTION 10)

Aggregate data on medicine consumption

In the field of psychotropic medicines, discrepancies between treatment recommendations and everyday clinical practice have frequently been highlighted (63).

At national or subnational (state or provincial) level, medicine consumption and expenditure are usually monitored using drug sales data. These data are routinely collected by independent sources from nationally representative samples of wholesalers and community pharmacies. Usually, the number of packages of each medicine sold is recorded, and data on total prescribing and expenditure are calculated. To allow comparisons to be made independently of differences in price, preparation and quantity per prescription, data are converted into defined daily doses (DDDs) per 1000 inhabitants per day. For each new therapeutic agent introduced into the market, WHO calculates the appropriate DDD, and a regularly updated list of all medications with the corresponding DDDs is accessible at www.whocc.no/atcddd. Aggregate data on medicine use can be obtained from many sources within the health-care system, including procurement records, warehouse drug records, pharmacy stock and dispensing records, medication error records and adverse drug reaction records. Aggregate data sources can be used to obtain a variety of information, for example (27):

- Which medicines are used most frequently and which most infrequently? Does actual medicine consumption match expected consumption according to morbidity records? What are the most frequent adverse drug reactions?
- Which are the most expensive medicines? On which medicines is most money spent? What are the most expensive therapeutic categories? What percentage of the budget is spent on certain medicines or classes of medicine?

As these analyses are based on aggregate rather than individual data, the DDD methodology measures medicine consumption but cannot provide information on individuals receiving a particular category of medicines. It is therefore not possible to draw individual-level inferences without giving rise to errors in interpretation (ecological fallacy). To overcome these limitations, it is possible to carry out analyses of databases with individual-level data. These databases, usually developed for managements, claims, administration and planning, cover large groups of individuals and generate data that are of value in pharmacoepidemiological research (64).

Although administrative databases with individual-level data are usually employed to describe the epidemiology of medicine use, they can also be used to investigate plausible associations between drug exposure and adverse or beneficial outcomes. This use presumes the possibility of linking different databases, for example a psychotropic medicine database covering individuals living in a defined catchment area and a second database with information on the outcome of interest.

District medical officers may use national or state medicine consumption statistics, if available, as well as analyses of administrative databases, for monitoring changes in prescribing behaviours over

time and for making comparisons with locally available data. They may also be interested in auditing prescribing habits in order to assess the coherence between what is recommended by evidence-based guidelines and what is actually done. It may therefore be of interest to develop monitoring systems that are able to collect information on medicine use, and, if feasible, to link these data with hard outcome indicators. The development of such infrastructures may be seen as a quality requirement for health-care systems that wish to hold themselves accountable.

Box 31. Example of how administrative databases may be used for pharmacovigilance purposes[1]

A pharmacoepidemiological study was carried out to investigate whether exposure to antipsychotics is associated with an increased risk of pulmonary embolism. The data used were retrieved from the regional health service administrative databases of Lombardy, Italy. These databases include:

- demographic and administrative information on all residents in the Lombardy region;
- all community (outside the hospital) prescriptions reimbursed by the regional health service;
- all public and private hospital discharge forms, with diagnoses according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

Exposure to antipsychotics was measured on the basis of prescriptions, while hospital discharge forms were used to measure non-fatal or fatal pulmonary embolism events during follow-up.

The analysis found that, compared with past use, current antipsychotic use more than doubled the risk of pulmonary embolism (odds ratio 2.31, 95% confidence interval 1.16-4.59), while recent use did not increase the risk. Both conventional and atypical antipsychotic exposure was associated with an increase in risk, and the concomitant use of both classes increased the risk by four times (odds ratio 4.21, 95% confidence interval 1.53-11.59).

[1]Source: http://www.biomedcentral.com/1471-244X/15/92/abstract.

Medicine utilization reviews

In addition to the development of permanent monitoring systems, district medical officers may carry out medicine utilization reviews, addressing specific questions related to the appropriateness of everyday prescribing. Indicators for reliably measuring aspects of health-provider behaviour in primary health-care facilities, irrespective of who collects the data, are available (27). WHO and the International Network for the Rational Use of Drugs, for example, developed a suite of indicators concerning medicine use, prescribing habits and important aspects of patient care (65).

Data may be collected retrospectively, from patient charts and other records, or prospectively, at the time a medicine is prepared or dispensed (27). Retrospective data collection may be quicker and is best accomplished away from the patient care areas and distractions. The advantage of a prospective review is that the reviewer can intervene at the time the medicine is dispensed to prevent errors in dosage, indications or interactions, or other mistakes. A particular example of this is the computerized systems used in some pharmacies; the computer warns the pharmacist if patient data entered into the computer fail to meet established criteria and requires them to correct the problem(s) noted. Such a system can also provide a large database for use retrospectively.

Box 32. Indicators commonly used to describe medicine use in health facilities[1]

- **Prescribing indicators**
  - average number of medicines per encounter
  - percentage of medicines prescribed by generic name
  - percentage of encounters with an antibiotic prescribed
  - percentage of encounters with an injection prescribed
  - percentage of medicines prescribed from essential medicines list or formulary
  - percentage of patients leaving without a medicine being prescribed.
- **Patient care indicators**
  - average consultation time
  - average dispensing time
  - percentage of medicines actually dispensed
  - percentage of medicines adequately labelled
  - patients' knowledge of correct dosage.
- **Health facility indicators**
  - availability of copy of essential medicines list or formulary
  - availability of key or essential medicines.

[1]Source: reference 65.

Data must be collected from a suitable random sample of charts or prescription records from the health-care facility, usually selected by pharmacy personnel but also by nurses or medical records personnel. The treatment of at least 30 patients, or 100 patients for common clinical conditions, should be reviewed per health facility or hospital. The larger the facility and the more practitioners, the larger the number of records needed for review and analysis.

Analysis of claims to reimbursement systems (where such systems exist) could be another source of information on prescriber practice. Data on how medicines are prescribed and regular reports are essential. Monitoring provides important feedback to initiate action.

Implementation of research initiatives

Research initiatives may be considered as strategies supporting a more appropriate use of psychotropic medicines. Multicentre, 'real-world', independent studies where investigators simultaneously act both as physicians and researchers may be powerful tools to stimulate a critical attitude towards prescribing habits. In this way, they may help introduce a pragmatic and more structured approach to the assessment of the benefits and harms associated with pharmacological treatments. By using multiple sites, comparisons of local data with data from other participating sites and with international standards, can be made. Additionally, producing knowledge from the field settings is considered a valuable tool to decrease the gap between the world of experimental studies and the reality of clinical practice. A more pragmatic approach to mental health is now illustrated by a number of studies carried out over the past decade (66). For example, Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) (67) and Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS) (68) are important groundbreaking studies with greater levels of pragmatism than in previous large mental health trials. The series of Tranquilização Rápida – Ensaio Clínic (TREC) (69, 70) trials further developed techniques in pragmatism within mental health.

Box 33. Example of pragmatic studies carried out in the real world of clinical practice[1]

Huf and colleagues carried out a randomized pragmatic trial to assess the effectiveness of intramuscular haloperidol versus IM haloperidol plus promethazine. Patients were recruited in a psychiatric emergency room in Rio de Janeiro, Brazil.

Raveendran and colleagues, using as comparator the same drug combination (IM haloperidol plus IM promethazine), assessed the effectiveness of IM olanzapine. Patients were recruited in emergency services of a general hospital psychiatry department in Vellore, south India.

These two studies are good examples of the concept of pragmatism:

- participants were selected on the basis not of a particular diagnosis but of a clinical presentation;
- patients were recruited in clinical practice settings;
- treatments were selected on the basis of being commonly and routinely used worldwide;
- clinicians were free to use varying doses according to clinical status and circumstances;
- clinically sound outcomes were used;
- the studies were not funded by industry (suggesting that the trials were motivated solely by the need to answer a question perceived as urgent and relevant).

It is probable that the broad entry criteria and soft follow-up assessments explain why these trials successfully recruited a large sample of patients with nearly complete follow-up. Similarly, the recruitment of typical patients, assessed with clinically sound outcome parameters, is the reason why the study's findings may be applicable to the routine care of patients with agitated or dangerous behaviour.

[1]Sources: references 70, 71.

Box 34. Example of a pragmatic study carried out in the real world of clinical practice to assess an intervention that involves family members in supervising medication administration[1]

A particularly interesting example of a simple, pragmatic, randomized trial was conducted in the psychiatry department of Lady Reading Hospital, Peshawar, Pakistan. It assessed the efficacy of an intervention consisting of:

- registration and recording of all people presenting with a diagnosis of schizophrenia/schizoaffective disorder from a geographically defined catchment area;
- training a key care supervisor, identified by the patient and usually a close relative, to administer and supervise the medication (collecting the medicine from the health facility, administering the correct dosage of all medication and recording adherence to treatment);
- uninterrupted drug supplies to provide drug treatment following a simple standardized treatment protocol;
- standardized monitoring of therapy and outcome.

A total of 110 individuals with schizophrenia or schizoaffective disorders were allocated to experimental intervention or to treatment as usual and followed up for 1 year. Participants in the experimental group showed better adherence (complete adherence: 67.3% vs 45.5%) and significant improvement in symptoms and functioning.

The authors concluded that a package of care based on a brief educational intervention for the families plus supervision and easy access to medication can be used to improve services for people with schizophrenia in LMICs.

[1]Source: reference 72.

PROMOTING TRAINING INITIATIVES FOR STAFF AND USERS ON CRITICAL APPRAISAL OF SCIENTIFIC EVIDENCE AND APPROPRIATE USE OF PSYCHOTROPIC MEDICINES (ACTION 11)

Critical appraisal skills

The acquisition of basic methodological skills in the critical assessment of research reports can significantly influence interpretation of the evidence base, which can in turn affect national guidelines, training materials and, ultimately, prescribing practices. For health-care professionals, enhancing skills in critical appraisal of the evidence base, linked to clinical guidelines and essential medicines lists, can help establish good prescribing habits. Training is more successful if it is problem-based, concentrates on common clinical conditions, takes account of previous knowledge, attitudes and skills, and is targeted to appropriate prescribing.

Critical appraisal has been defined as the systematic evaluation of clinical research papers in order to increase the ability to critically assess information. It aims to provide skills to answer the following questions:

- Did this study address a clearly focused question?
- Did the study use valid methods to address this question?
- Are the valid results of this study important?
- Are these valid, important results, applicable to my patient or population?

Critical appraisal skills should be included in national undergraduate curricula. If this is not the case, district medical officers might consider offering learning and training modules, based on available resources, to all actors involved in the prescribing cycle. An organization that may offer methodological support is Cochrane, a global independent network of health practitioners, researchers, patient advocates and others, responding to the challenge of making the vast amounts of evidence generated through research useful for informing decisions about health. Cochrane is a not-for-profit organization with collaborators from more than 120 countries working together to produce credible, accessible health information that is free from commercial sponsorship and other conflicts of interest.

Box 35. Selection of high-quality online resources and tools freely available on the Cochrane Collaboration website

- Centre for Evidence-Based Medicine, Toronto, Canada: http://ktclearinghouse.ca/cebm
- EBM Tools, at the University of Oxford: http://www.cebm.net/category/ebm-resources/tools/
- EQUATOR (Enhancing the QUAlity and Transparency Of health Research) Network provides central access to reporting guidelines: http://www.equator-network.org/index.aspx
- SUPPORT (Supporting Policy relevant Reviews and Trials), coordinated by the Norwegian Knowledge Centre for the Health Services; Chinese, French, Portuguese and Spanish translations are also hosted by PAHO/WHO: http://www.globalhealth.no/projects/the-support-collaboration-supporting-policy-relevant-reviews-and-trials

Box 36. Efficacy of teaching critical appraisal skills to health professionals[1]

A Cochrane review was carried out to assess whether teaching critical appraisal skills to health professionals led to changes in processes of care, patient outcomes, health professionals' knowledge of how to critically appraise research papers, or all three.

The review included three studies involving 272 people. It found that low-intensity critical appraisal teaching interventions in health-care populations may result in beneficial gains. However, there was a lack of quality evidence on whether teaching critical appraisal skills led to changes in the process of care or to changes in patient outcomes. The authors pointed out that improvements are required in research examining the effectiveness of interventions in health-care populations, and that rigorous randomized trials employing interventions using appropriate adult learning theories should be designed and carried out.

Another review that included randomized and non-randomized evidence found that multifaceted, clinically integrated interventions with assessment led to improvements in knowledge, skills and attitudes. Interventions improved critical appraisal skills and integration of results into decisions, and improved knowledge, skills, attitudes and behaviour among practising health professionals. Considering single interventions, evidence-based health-care knowledge and attitudes were similar for lecture-based ver-

sus online teaching. Journal clubs appeared to increase clinical epidemiology and biostatistics knowledge and reading behaviour but not appraisal skills. Among practising health professionals, interactive online courses with guided critical appraisal significantly increased knowledge and appraisal skills. A short workshop using problem-based approaches, compared with no intervention, increased knowledge but not appraisal skills.

[1]Sources: references 73, 74.

Box 37. Teaching evidence-based medicine in Tehran, Islamic Republic of Iran[1]

A study comparing two different techniques of teaching evidence-based medicine was carried out in the Tehran University of Medical Sciences. The study randomly allocated 86 medical faculty members to the intervention group and 84 to the control group. The intervention group consisted of 12 two-day programmes (6 hours per day). Each session consisted of conferences followed by small-group discussions and training-group activities. A traditional conference method was used in the control group.

The study found that conference integrated with small-group discussion was associated with improved knowledge, attitude toward evidence-based medicine, and skills as measured by improvement in critical appraisal, using evidence-based resources, addressing patients' values in clinical practice, and correct implementation of the level of evidence.

[1]Source: reference 75.

Training and continuing education

Basic training in appropriate use of psychotropic medicines for medical and paramedical students is a prerequisite for the establishment of good future prescribing habits. Further, continuing education of health-care professionals is another step towards the establishment and maintenance of good prescribing habits. The term "continuing education" refers to activities that serve to maintain, develop or increase knowledge, skills and performance expertise needed for professional development and to ensure optimal patient care.

Continuing medical education is a requirement for licensure of health-care professionals in many highly developed countries. It is usually not limited to professional medical or paramedical personnel but may also include people in the informal sector such as medicine retailers. Unfortunately, like other forms of education, it may be dependent on the support of pharmaceutical companies in the absence of adequate public funds. Continuing education funded in this way has been shown to be biased, often failing to provide a balanced and critical view of the beneficial and harmful consequences of medicines. Governments should therefore support efforts by university departments and national professional associations to provide independent continuing education.

Box 38. Example of the relationship between information sources used by the physicians and the quality of prescribing[1]

A cross-sectional study of 405 primary care physicians was carried out in Galicia, Spain. Using a postal questionnaire survey, information was collected on physicians' education, specialization and types of available information sources. Information on prescribing habits was also collected. The study found that the overall quality of prescribed medicines increased as the physician placed more reliance on independent sources of information, and decreased with greater reliance on sources of information from the pharmaceutical industry, including visits from pharmaceutical representatives.

Another survey conducted in 200 English practices was carried out to describe the attitudes and behaviour of general practitioners who reported seeing drug company representatives frequently. The survey found that frequent contact with drug company representatives was significantly associated with a greater willingness to prescribe new drugs and to agree to patients' requests to prescribe a drug that is not clinically indicated. Interestingly, it was also observed that general practitioners who see drug representatives most often tend to be those who are isolated from their colleagues (single-handed practitioners and those not involved in general practitioner training) and to work in deprived areas.

[1]Sources: references 76, 77.

District medical officers should support - and make every effort to regularly organize and maintain - independent education initiatives on the appropriate use of psychotropic medicines, with special attention to health-care providers working in rural or deprived areas and to people in the informal sector if appropriate. These initiatives, linked to critical appraisal skills (the ability to assess information on medicines critically), clinical guidelines and essential medicines lists, can help to establish and maintain good prescribing habits.

Experience has shown that there is a greater impact on behaviour when specific prescribing and dispensing behaviour is targeted, groups are small, known experts are involved in teaching, and training is fol-

Box 39. Effect of medical education on health professional behaviour and health-care outcomes[1]

A landmark systematic review of randomized controlled trials of formal didactic and interactive education activities included 14 studies and 17 interventions. Nine generated positive changes in professional practice, and three out of four interventions altered health-care outcomes in one or more measures.

Seven studies providing information suitable for re-analysis found no significant effect of standard educational methods; however, interactive and mixed educational sessions were associated with a significant effect on practice. Techniques such as case discussion, role-play and hands-on practice sessions were effective in changing the performance of health-care professionals. Sequenced sessions of learn-work-learn, in which education may be translated into practice and reinforced at a further session, had a positive impact.

These findings were more recently reinforced by a Cochrane review which included randomized controlled trials of different educational strategies that reported an objective measure of professional practice or healthcare outcomes.

Eighty-one trials were included in this review. It suggested that educational meetings alone can only marginally improve professional practice and the achievement of treatment goals by patients. The effect on professional practice tended to be small but varied between studies, and the effect on patient outcomes was generally less. It appeared that mixed interactive and didactic education was more effective than either alone, and that the effects were less for more complex behaviours and less serious outcomes.

[1]Sources: references 78, 79.

lowed up with specific feedback on actual prescribing practices (preferably through on-site supervision). In recent years the internet has dramatically expanded opportunities for flexible, convenient, interactive provision of computer-mediated education activities, and online learning is gaining in popularity as an alternative form of education. District medical officers may consider employing the following tools:

- course information, notice board, timetable;
- curriculum map;
- teaching materials such as slides, handouts, articles;
- communication via email and discussion boards;
- formative and summative assessments;
- student management tools (records, statistics, student tracking); and
- links to useful internal and external websites, including library, online databases and journals.

Tools can be synchronous (chat room and desktop conferencing) and asynchronous (online discussion, email, bulletin board or forum, video and audio streaming and online testing.

The strengths of web-based education technology include time flexibility, convenience and the absence of transportation problems. In addition, the new technology has also played an important role in easing the shortage of educators. However, there are also challenging issues, including access to the internet in the first instance, poor information literacy which may result in inappropriate operation of web learning, isolation of students with possible loss of the social process of learning, and resources required to develop learning materials.

Providing access to unbiased information on psychotropic medicines

In many countries, continuing education and other training activities are heavily supported by pharmaceutical companies. Moreover, information supplied by the pharmaceutical industry through mailings, visits by drug company representatives and industry-sponsored formularies is often the only type of information available to prescribers. Unbiased information on psychotropic medicines is, however, available and accessible. The WHO Model List of Essential Medicines and WHO and national formularies are reliable, independent sources of information to which health-care workers can refer. Additionally, the Cochrane Library offers free access to residents in more than 100 LMICs (http://www.cochranelibrary.com/help/access-options-for-cochrane-library.html). Cochrane reviews include plain-language summaries (PLS). The PLS is a stand-alone summary of the systematic review that conveys succinctly and clearly the key questions and findings of the review. It is written in plain English, without technical terms or jargon, and can be understood by most readers without a university education.

In January 2002, WHO together with major publishers launched the Health Internetwork Access to Research Initiative (HINARI), which provides LIMCs with access to one of the world's largest collections of biomedical and health literature (80). Eligibility for access may be checked at: http://www.who.int/hinari/en/.

Box 40. A study on the use of the Health Internetwork Access to Research Initiative (HINARI) in south-western Nigeria[1]

A survey of knowledge and usage pattern of HINARI by clinicians and researchers in tertiary health institutions was conducted in south-western Nigeria. The descriptive cross-sectional survey was conducted among 1150 clinicians and researchers in the 12 tertiary health institutions that had access to HINARI. A standardized, self-completed, 31-item questionnaire was used for data collection.

The majority of respondents were aware of HINARI (72%). Only 35%, however, had formal training in its use. Sixty-eight percent (68%) had actually used HINARI resources and 62% of these did so during the month preceding the study. The most frequently used HINARI resources were MEDLINE/PubMed (53%), full-text journal articles (55%), and reference materials (28%).

The authors concluded that, although knowledge and use of these resources were high, clinicians and researchers were not deriving full benefits from HINARI because few had received training in its use.

[1]Source: reference 81.

District medical officers should consider organizing initiatives to increase knowledge and use of HINARI resources, including specific training courses. If feasible, the impact of HINARI on the behaviour of health-care and on patient outcomes should be investigated.

Box 41. Cochrane as an example of independent sources of information on medicines[1]

Cochrane is a global independent network of researchers, professionals, patients, carers and people interested in health. Users may access patient-centred summaries of the content of Cochrane reviews: http://www.cochrane.org/evidence.

Consumers may also access initiatives on learning to use the evidence: http://consumers.cochrane.org/.

[1]Sources:
Cochrane Collaboration : http://www.cochrane.org/
Cochrane Database of Systematic Reviews: http://www.cochranelibrary.com/

Box 42. The International Society of Drug Bulletins as an example of independent sources of information on medicines

The International Society of Drug Bulletins (ISDB) is a worldwide network of bulletins and journals on drugs and therapeutics that are financially and intellectually independent of the pharmaceutical industry. It was founded in 1986, with the support of the WHO Regional Office for Europe.

Drug bulletins aim to improve health-care quality by providing relevant information about treatments (i.e. reliable, comparative and adapted to users' needs) and promoting more rational, informed decisions about their use. The primary audience for most bulletins is doctors and pharmacists but also, and increasingly, consumers. ISDB members often also deal with broader drug policy issues.

A list of bulletins belonging to the ISDB can be found at: http://www.isdbweb.org/members/bulletin_index

Public education about the role and limits of psychotropic medicines

According to WHO, without sufficient knowledge about the risks and benefits of using medicines and when and how to use them, people will often not get the expected clinical outcomes and may suffer adverse effects. This is true for both prescribed medicines and medicines or supplements used without the advice of health professionals. Moreover, education of consumers is neglected in many parts of the world. This is of special concern in developing countries, where medicines are widely available without prescription from a variety of sources and where promotion of medicines is frequently inappropriate and not well regulated.

Education campaigns that take account of cultural beliefs and the influence of social factors can be considered a useful strategy for increasing knowledge on the appropriate use of psychotropic medicines. As traditional concepts about mental disorders may also affect acceptance of and adherence to pharmacological treatments, education campaigns should try to understand people's views on mental disorders and the proposed treatments. Among examples of commonly held cultural beliefs are that psychotropic medicines are unnatural and poisonous substances or that they make the body unnaturally hot or cold and weaken or enervate patients (82). Other groups, such as traditional healers and those selling medicines, need to be included in a comprehensive educational strategy to improve medicine use. Education campaigns can also be conducted in schools.

Box 43. Efficacy of school-based mental health literacy programmes[1]

Mental health literacy has been defined as "knowledge and beliefs about mental disorders which aid their recognition, management or prevention".

A 2013 systematic review of studies looking at the impact of school mental health literacy programmes found insufficient evidence for definitively claiming a positive impact on knowledge improvement, attitudinal change or help-seeking behaviour. However, individual studies suggested some beneficial effect on these variables.

A school-based mental health programme in Canada provides an example. A study was conducted to assess the impact of a recently developed school-based mental health literacy resource (Mental Health and High School Curriculum Guide). The Guide is a mental health literacy resource consisting of six modules that are delivered in 10–12 hours of class time through a mix of didactic instruction, group discussion, group activities, self-directed learning and video presentations. Topics covered include stigma and mental illness, understanding mental health and mental illness, information on specific mental illness, first-voice experiences and impact of mental illnesses on individuals and families, help-seeking and the importance of positive mental health.

Evaluation of mental health literacy (knowledge/attitudes) among 265 high-school students was completed before and after classroom implementation and at 2-month follow-up. Students' knowledge significantly improved between the first and second tests and was maintained at follow-up. Similarly, attitudes improved significantly between first and second tests and was significantly higher at follow-up than at baseline.

The Guide can be obtained at: www.teenmentalhealth.org.

[1]Sources: references 83–85

District medical officers should consider establishing systems of information on medicines, and empowering consumers to take responsible decisions about their treatment. Within a system of information on medicines, particular attention should be paid to medicine advertisement and promotion. All promotional claims should be reliable, accurate, truthful, informative, balanced, up-to-date, capable of substantiation and in good taste.

Consumers should be provided with adequate instructions on the benefits and harms associated with the use of psychotropic medicines. They should familiarize themselves with the use of independent sources of information on medicines, including the Cochrane Collaboration and the International Society of Drug Bulletins mentioned previously.

A PRACTICAL APPROACH TO IMPROVING ACCESS TO MEDICINES FOR MENTAL DISORDERS

This report has discussed the following key priority actions for improving access to psychotropic medicines:

Action 1 Developing a medicine selection process
Action 2 Promoting information and education activities for staff and users on the selection process
Action 3 Regulating psychotropic medicine availability
Action 4 Implementing a reliable health and supply system
Action 5 Ensuring quality of psychotropic medicines
Action 6 Developing a community-based system of mental health care
Action 7 Developing policies on affordability of medicines
Action 8 Developing pricing policies and fostering a sustainable financing system
Action 9 Adopting evidence-based guidelines
Action 10 Monitoring the use of psychotropic medicines
Action 11 Promoting training initiatives for staff and users on critical appraisal of scientific evidence and appropriate use of psychotropic medicines

These actions may be organized as a function of the health-care level. Four different levels have been considered, three belonging to the supply side and one to the demand side:

- international
- national or subnational (state or provincial)
- district health service
- individual, household or community (demand side) (9).

Priority actions may therefore be inserted into a 4 x 4 framework to provide better understanding of the level at which each should be activated; see Table 6.

Table 6. Actions for improving access and appropriate use of medicines for mental disorders

Actions are organized as a function of the four components of access - selection, availability, affordability and appropriate use - and across four different health-care levels, three on the supply side and one on the demand side (4 x 4 access framework)

Side	Level	ACCESS COMPONENTS			
		SELECTION	AVAILABILITY	AFFORDABILITY	APPROPRIATE USE
Supply	International	Development and regular update of the WHO Model List of Essential Medicines (Action 1)		Developing policies on medicine affordability (Action 7)	Adopting evidence-based guidelines (Action 9)
	National or subnational	Development of a medicine selection process that includes psychotropic medicines (Action 1)	Regulating psychotropic medicine availability (Action 3) Implementing a reliable supply system (Action 4) Ensuring quality of psychotropic medicines (Action 5) Developing a community-based system of mental health care (Action 6)	Developing pricing policies and fostering a sustainable financing system with affordable medicine prices (Action 8)	National adaptation of international evidence-based guidelines or development of national evidence-based guidelines (Action 9) Monitoring the use of psychotropic medicines (Action 10) Inclusion of critical appraisal of scientific evidence and training in appropriate prescribing in undergraduate curricula (Action 11)
	District health service	Local implementation and adaptation of national or international psychotropic medicines lists (Action 1) Promotion of information and education initiatives for professionals on the selection process (Action 2)	Implementation of strategies to provide mental health care in remote and rural areas and ensure distribution of medicines at this level (Action 6)		Local implementation and adaptation of evidence-based guidelines (Action 9) Monitoring the use of psychotropic medicines (Action 10) Promotion of education and training initiatives on critical appraisal of scientific evidence and appropriate use of psychotropic medicines (Action 11)
Demand	Individual, household or community	Promotion of information and education initiatives for users on the selection process (Action 2)	Promotion of initiatives on the acceptability of mental health care, including medicines for mental disorders (perception to be appropriate, attitudes and expectations) (Action 6)		Promotion of public education initiatives about the role and limits of psychotropic medicines (Action 11)

SITUATION ANALYSIS

In order to improve a poorly functioning access system, an accurate situation analysis should be carried out. Table 6 may be used as a guide to defining, as a first step, the health-care level at which action would be appropriate. As a second step, a careful inspection of the existing functions of the access system should be carried out, assessing which of the actions outlined above have never been activated and which are functioning but need to be reinforced or developed further.
For example, a situation analysis conducted at the level of the district health service would need to assess the following aspects:

Selection of psychotropic medicines

- Is there a national list of registered medicines?
- Which psychotropic medicines are included?
- Is there a national list of essential medicines?
- Which psychotropic medicines are included?
- Has a list of essential psychotropic medicines been locally implemented and adapted to meet the specific mental health needs of the district health service?
- Are there information and education initiatives for staff and the public on local implementation of the national list of essential psychotropic medicines?

Availability of psychotropic medicines

- Are psychotropic medicines available at the points where they are needed?
- Are there major losses due to expiry of shelf-life or theft?
- Are psychotropic medicines purchased and used in a system of good quality?
- Are local quality assurance programmes adequate?
- Which initiatives have been implemented to provide mental health care in remote and rural areas and ensure distribution of medicines at this level?

Affordability of psychotropic medicines

- What are the prices of psychotropic medicines? Are there hidden costs that drive up the prices at local level?

Appropriate use of psychotropic medicines

- Have evidence-based guidelines been locally developed or implemented?
- Are there training initiatives for staff on critical appraisal of scientific evidence and appropriate use of psychotropic medicines?
- Are there drug utilization data to monitor whether psychotropic medicines are used appropriately?

Box 44. Assessing poor access to psychotropic medicines in a hypothetical country[1]

Poor access is caused by a variety of problems, ranging from unavailability of essential psychotropic medicines in the public health-care delivery system to circulation of poor-quality brand-name products in the private sector. There are many opinions but few clear ideas on the causes of poor access. Despite a functioning national health insurance system, consumers always pay an additional fee for drugs when collecting medicines from both public and private pharmacies. For mental disorders there is the additional problem that only inpatient treatments are covered, and the capacity of the mental health-care delivery system is grossly inadequate.

To improve this dismal situation, a joint task force was established by the Ministry of Health (MOH), drawn from its own staff, a large NGO that provides mental care, the Medical University, the Medical Association and the Pharmacists' Association. It was decided to carry out a three-week limited assessment using existing information sources but paying extra attention to the selection of psychotropic medicines for the public sector, to their affordability, and to the financing of mental health care and its drug needs.

Although it was felt that enough in-country expertise was available for most of the tasks, it was decided to request the assistance of WHO experts in the area of clinical pharmacology (with specific knowledge of psychotropic treatment) and of a health economist to provide extra expertise in the areas of drug pricing and financing.

To maximize efficiency, a set of key documents was made available well in advance to each team member, including:

- National Essential Medicines List
- National Standard Treatment Guidelines
- NGO Standard Treatment Guidelines
- procurement policy of the Central Medical Store (CMS)
- price catalogue of the CMS
- reimbursement policy of the National Health Insurance
- a survey of prices of a basket of drugs (including three psychotropic medicines) in commercial pharmacies in the capital, carried out by a health activists' group.

The task force decided that only three rapid surveys could be carried out within the limited time and resources available, the results of which would have to be available at the time of the assessment:

- a price survey of essential psychotropic medicines in the public sector;

- a price survey of essential psychotropic medicines in the private sector;
- a psychotropic medicines prescribing survey in a sample of outpatient departments of mental health institutions.

Team members were asked well in advance whether they would have additional information needs. To guarantee independence, the MOH decided to use its own resources and not to ask international agencies to fund the assessment, except for the two experts to be made available by WHO. As team-leader, it was decided to invite an independent international health expert with considerable experience in strengthening mental health systems in a variety of developing countries. The expert was asked to be fully involved in all stages of preparation and implementation of the assessment.

The three-week assessment by five experts consisted of a range of key informant interviews, study of documents, analysis of survey results, and focus group discussions with patients and their family members in the five regions of the country. The assessment ended with a two-day workshop entitled "Better access to mental health and essential psychotropic medicines: the way forward", which received considerable attention from the local media.

[1]Source: reference 13

IMPLEMENTING INTERVENTION PROGRAMMES

The situation analysis described above will allow for a thorough analysis and understanding of the main problems in a psychotropic medicines access system. Detailed analysis of the findings can assist in identifying the major problems and their causes, and potential solutions.

According to WHO, the following steps should be followed to improve access (13):

- Once the main problems and their causes have been identified, goals and priority objectives can be defined (for example improving selection, affordability and financing of essential psychotropic medicines; improving the appropriate use by health professionals).
- The selection of intervention programmes to achieve the defined objectives is more complex, as it involves choosing from many different intervention options. The systematic assessment should justify the choices and serve as the basis for decisions. Broad consultation and careful consideration of structural constraints are necessary.
- Any intervention programme needs an overall implementation plan or master plan. The plan may cover a 3- to 5-year period.
- Selecting appropriate indicators of progress will enable monitoring and evaluation of the impact of the interventions. Monitoring is a way to continuously review implementation of the activities and determine whether targets are likely to be met.

APPROPRIATE PRESCRIBING OF MEDICINES FOR MENTAL DISORDERS

GENERAL PRINCIPLES

The decision to prescribe a pharmacological treatment must take into consideration the potential risks and benefits to each individual. Health-care providers should discuss these potential risks and benefits with patients, family members and/or carers, adopting a clear and empathic language, sensitive to age, sex and cultural differences. Privacy and confidentiality should always be preserved, and disclosure of distressing information should be managed with sensitivity and respect. Information on health status should be provided to individuals in terms that they can understand.

Health-care providers should be aware of the important role of medicines in the doctor–patient relationship and should make an effort to involve each patient collaboratively in relation to any prescribed medication. The psychological implications of receiving a pharmacological treatment should be discussed and taken into account.

Most psychiatric disorders can be effectively treated by a combination of pharmacological and non-pharmacological interventions. The decision to prescribe a psychotropic agent never implies that psychological and/or psychosocial interventions are not indicated: evidence has consistently shown that combining medicines with psychosocial interventions tends to be associated with better outcomes. Health-care providers should not limit therapeutic strategy to medications, and it should not be suggested to patients that modifications of thought, mood and conduct can be achieved by pharmacological means alone. Articulated, comprehensive and individualized treatment plans represent the best therapeutic approach. The health-care provider should determine the therapeutic goals for each affected person and create a management plan that respects the treatment preferences of that person (and those of a carer, if appropriate).

In general, prescriptions should not be issued before detailed physical assessment. Health-care providers should take a medical history, history of the presenting complaints and family history. They should always investigate current and past use of medicines and note any history of substance abuse. A past history of alcoholism, for example, is often present in individuals liable to misuse of drugs; alcohol or drug abuse or dependence should prompt particular care in prescribing medicines with dependence potential.

When prescribing certain medicines for mental disorders (see sections below on individual drug classes), health-care workers should be aware that monitoring of a wide range of health parameters is generally recommended, at baseline and during treatment. These parameters include body weight, blood pressure, electrocardiogram, full blood count, urea and electrolytes, creatinine phosphokinase, liver function, blood glucose, lipid pattern and prolactin. If these examinations are not feasible, health-care providers should ask the patient and/or family member about the existence of cardiovascular, renal or hepatic abnormalities and whether pharmacological treatments for these medical conditions have been prescribed and taken.

It should be clear to the patient that treatment will continue for a pre-planned period of time, which may be related to the pharmacological properties of the medicines used and/or to the condition under treatment. Clear instructions should be provided on how and when medicines should be taken; written instructions may increase treatment adherence. Health-care providers should encourage patients to ask questions and raise concerns about treatment and should address these fully, giving realistic hope for better functioning and recovery. This is particularly relevant in communicating the importance of medication in preventing relapse.

Finding the appropriate dose of pharmacological treatments for a particular individual should be done gradually, especially in elderly patients, adolescents and people with medical comorbidities. The minimum effective dose should be prescribed, based on an assessment of how much of the drug is required to affect the target symptoms.

Patients should be informed about possible side-effects of treatment and measures to manage those side-effects (e.g. reduction in the dose), and they should be reassured that some of the side-effects are only temporary. Health-care providers should be aware of all the substances, both medical and nonmedical, being taken by patients and of the possible interactions; for example, alcohol and benzodiazepines should not be taken concurrently.

Health-care providers should know that some medicines for mental disorders are under international control, i.e. are regulated by the Convention on Psychotropic Substances, 1971 (United Nations). In addition, the use of some medicines may be under national control. International, national, regional and local regulations must be strictly followed.

Health-care providers should regularly monitor medicine use, asking specifically how much of the medicine has been taken. Adherence to treatment, which is essential for optimal response, varies considerably but can be improved by good patient education and by responding to patients' questions. Treatment effects and outcomes, including drug interactions (with alcohol, over-the-counter medication and complementary/traditional medicines) and adverse effects should also be regularly monitored.

In the choice of a specific medicine, health-care providers should consider its cost, availability and continuity of supply. In situations where continuity of supply may be frequently interrupted, it may be better to avoid the use of some medicines.

Health-care providers should be aware that a history of suicidal thoughts or attempts is an important indication of possible suicidal behaviour. Patients with such history should be specifically asked about suicide; if it is a possibility, health-care providers should use medicines that are safe in overdose, limit the quantity of medicines prescribed and establish a treatment regimen in which there is frequent clinical monitoring as well as monitoring by family members and friends.

Psychotropic medicine should be discontinued gradually (by 25% of the dose per week), unless otherwise indicated (e.g. if there are serious adverse effects or if antidepressants need to be discontinued in a bipolar disorder with mania).

In general, polypharmacy – the concurrent use of two or more medicines belonging to the same phar-

macological class (for example, two or more antipsychotics or two or more antidepressants) – should be avoided.

At follow-up, the health-care provider should reassess the patient's expectations and understanding of treatment, clinical status and adherence to the treatment and should correct any misconceptions. Treatment effects and outcomes, drug interactions and adverse effects of treatment should be continually monitored; if necessary, treatment should be appropriately adjusted.

In elderly individuals, medicines should be prescribed with caution. The metabolic changes that occur with ageing, and the concomitant use of medicines for various medical conditions, make elderly people more susceptible to side-effects. Research shows that four out of five people aged over 75 years take at least one medicine and 35% take four or more medicines. It is therefore generally suggested that a dose of between one half and one third of the normal adult dose be prescribed for elderly individuals. Health-care providers should also consider that older people may have practical problems that interfere with the optimal use of medicines, including difficulty in remembering to take medications, reading labels, hearing instructions from health-care professionals, opening bottles, breaking tablets, handling medicines, swallowing tablets or capsules, and scheduling different medications throughout the day. Potential risks for the fetus or baby must be assessed when providing medicines to a pregnant or breastfeeding woman. Babies of breastfeeding women on medications must be monitored for adverse effects or withdrawal; comprehensive examinations may be required. However, it is also important to consider the possible effect of relapse on the well-being of mother and baby if medication is reduced or stopped medication.

Health-care providers should ensure that all individuals are treated in a holistic manner, so that the mental health needs of people with physical disorders are met, as well as the physical health needs of people with mental disorders.

PRACTICAL PRINCIPLES FOR ANTIDEPRESSANT USE

Depression is a condition characterized by episodes of lowered mood, lack of energy and decreased activity. Capacity for enjoyment, interest and concentration is reduced, and marked tiredness after even minimum effort is common. Sleep is usually disturbed and appetite diminished. Self-esteem and self-confidence are almost always reduced and, even in mild depression, some ideas of guilt or worthlessness are often present. The lowered mood varies little from day to day, is unresponsive to circumstances and may be accompanied by so-called "somatic" symptoms, such as loss of interest and pleasurable feelings, waking in the morning several hours before the usual time, depression worst in the morning, marked psychomotor retardation, agitation, loss of appetite, weight loss and loss of libido. Although depressive feelings are common, especially after setbacks in life, depressive disorder is diagnosed only when the symptoms reach a threshold and last at least two weeks. Depression must be distinguished from the states of subjective distress and emotional disturbance, possibly interfering with social functioning and performance, that arise in the period of adaptation to a significant life change or stressful event (e.g. the death of a loved one).

Antidepressants are effective in around 60–70% of individuals with moderate to severe depression, although more than 30% of patients are placebo responders. Antidepressants may take 6–8 weeks to have a full therapeutic effect. Their efficacy has been demonstrated in clinical trials conducted in individuals with moderate to severe depression only; efficacy in mild depression is unproven.

According to the WHO EML, essential medicines for depressive disorders are amitriptyline and fluoxetine. Amitriptyline is indicated as an example of the class for which there is the best evidence for effectiveness and safety and represents tricyclic antidepressants.

According to the mhGAP Intervention Guide, health-care providers should consider the prescription of an oral antidepressant for patients with moderate to severe symptoms, functional impairment or an illness of long duration. If more than one antidepressant is available, the most suitable agent for each patient should be chosen on the basis of the following considerations:

- **Inclusion in the WHO EML.** This list includes the most efficacious, safe and cost-effective medicines.
- **Past history of antidepressant responsiveness.** If a patient has already responded well to a specific agent, without intolerable side-effects, that agent might be chosen; if a patient failed to respond to a specific agent, or had intolerable side-effects, that agent should generally not be prescribed again.
- **Medical comorbidities.** If a patient suffers from specific medical problems, some agents might be better avoided (e.g. amitriptyline should be avoided in elderly patients with cardiac problems; venlafaxine should be cautiously prescribed in patients with high blood pressure).
- **Subjective impact of adverse reactions.** The subjective impact of side-effects (e.g. the perceived relevance of sexual dysfunction varies between males and females and in different age groups) should be taken into consideration.
- **Costs.** Costs may vary according to the health-care system in which antidepressants are prescribed.
- **New/old agents.** As a general rule, it is wise to prescribe established medicines, since the side-effect profile of new medicines becomes clear only after years of use.

Box 45. mhGAP evidence-based recommendation: role of antidepressants and benzodiazepines[1]

Antidepressants should not be considered for the initial treatment of adults with mild depressive episode. Tricyclic antidepressants or fluoxetine should be considered in adults with moderate to severe depressive episode/disorder.

Neither antidepressants nor benzodiazepines should be used for the initial treatment of individuals with complaints of depressive symptoms in the absence of a current/previous depressive episode/disorder.

[1]Source: WHO mhGAP Evidence Resource Centre: http://www.who.int/mental_health/mhgap/evidence/en/

While tricyclic antidepressants are toxic in overdose, fluoxetine and other selective serotonin-reuptake inhibitors (SSRIs) are less dangerous and may be prescribed in patients at risk of self-harm. To avoid overdoses, people at imminent risk of self-harm/suicide should have access to only limited supplies of antidepressants (e.g. one week's supply at a time). Health-care providers should be aware that the risk of self-harm may increase as depression lifts and energy returns with treatment; it may be valuable to offer psychological support by scheduling follow-up visits at regular intervals.

Treatment effectiveness should be assessed after 6–8 weeks. If no improvement is seen after 8 weeks, the health-care provider should review the diagnosis (including comorbid diagnoses) and check whether medication has been taken regularly. The possibility of increasing the dose or of switching to another antidepressant should be discussed with the patient; if antidepressants of different classes are available, a change of medicine class is generally recommended. If treatment adherence is a major problem, the possibility of switching to another antidepressant that may be better tolerated should be discussed. If adverse reactions are a major problem, the possibility of reducing the dose should be discussed; if they persist despite a dose reduction, a switch to another antidepressant with a different pattern of adverse reactions may be considered.

A switch from one antidepressant to another should be undertaken with caution. Health-care providers should gradually reduce the dose of the first antidepressant while gradually increasing the dose of the new agent.

As a general rule, health-care providers should not prescribe two antidepressants simultaneously: potential dangers include the development of serotonin syndrome (restlessness, diaphoresis, tremor, shivering, myoclonus, confusion, convulsions).

Depressive episodes in patients with bipolar disorder (bipolar depression) generally respond to the same treatment as unipolar depression. However, antidepressant medicines may induce a switch from depression to mania. In patients with bipolar depression, health-care providers should prescribe antidepressants in association with a mood stabilizer – a combination that reduces the risk posed by switching. The risk of switching has been shown to be higher with tricyclic antidepressants than with SSRIs.

Box 46. mhGAP evidence-based recommendation: role of medicines in bipolar depression[1]

Antidepressant medicines, always in combination with a mood stabilizer (lithium or valproate), may be considered in the treatment of moderate or severe depressive episodes of bipolar disorder. Selective serotonin reuptake inhibitors (fluoxetine) should be preferred to tricyclic antidepressants.

[1]Source: WHO mhGAP Evidence Resource Centre: http://www.who.int/mental_health/mhgap/evidence/en/

People receiving antidepressants should be warned about the possibility of discontinuation/withdrawal symptoms if doses are missed and told that these symptoms, while usually mild and self-limiting, can occasionally be severe, particularly if the medication is stopped abruptly. They should be reassured, however, that antidepressants are not addictive.

After an acute episode has resolved, health-care providers should consider discontinuing antidepressant medication when the patient has (a) had no, or minimal, depressive symptoms for 9–12 months, and (b) been able to carry out routine activities for that time period. Discontinuation of treatment should be gradual, with doses being tapered over 2–3 months.

Box 47. mhGAP evidence-based recommendation: duration of antidepressant treatment[1]

In an adult patient with depressive episode/disorder who has benefited from initial antidepressant treatment, the treatment should not be stopped sooner than 9–12 months after recovery. Treatment should be regularly monitored, with special attention to treatment adherence. Frequency of contact with the health-care provider should be determined by treatment adherence, severity of the episode/disorder and local feasibility issues.

[1]Source: WHO mhGAP Evidence Resource Centre: http://www.who.int/mental_health/mhgap/evidence/en/

Tricyclic antidepressants should generally be avoided in older people, as they are associated with postural hypotension, cardiac conduction abnormalities and arrhythmias. If possible, SSRIs are first choice. Health-care providers should ask the patient and/or family member about the existence of cardiovascular abnormalities and whether drug treatments for cardiac problems have ever been prescribed and taken. If there is arrhythmia or other cardiac problem, health-care providers should obtain an electrocardiogram before antidepressant treatment is initiated.

In adolescents there is little evidence that tricyclic antidepressants are efficacious and, given their side-effects and the risks of toxicity in overdose, they are generally not recommended. Similarly, the balance between benefit and harm is considered unfavourable for most SSRIs, except fluoxetine, which has been shown to be effective for treating depressive illness in adolescents.

Box 48. mhGAP evidence-based recommendation: antidepressants for adolescents with depression[1]

When psychosocial interventions prove ineffective in adolescents with moderate to severe depressive episode/disorder, fluoxetine (but not other selective serotonin-reuptake inhibitors or tricyclic antidepressants) may be offered. The intervention should be offered only under supervision by a specialist

[1]Source: WHO mhGAP Evidence Resource Centre: http://www.who.int/mental_health/mhgap/evidence/en/

During the first month of treatment, adolescents receiving fluoxetine should be monitored frequently (ideally once a week) for emergence of suicidal ideas. Adolescent patients and their parents should be warned about the increased risk of suicidal ideas and told to make urgent contact if they notice such features. Health-care providers should balance the possible increased risk against the well-established risk of suicide in untreated depression.

Health-care providers should avoid prescribing antidepressants during pregnancy and breast-feeding. However, if psychosocial treatments are ineffective, and maternal depression is a major concern, an antidepressant may be prescribed at the lowest effective dose.

Box 49. mhGAP evidence-based recommendation: antidepressants in women with depressive episode who are planning a pregnancy or are pregnant or breastfeeding[1]

If drug treatment is required in a woman with depressive episode who is planning a pregnancy or who is pregnant or breastfeeding, tricyclic antidepressants or fluoxetine should be considered.

[1]Source: WHO mhGAP Evidence Resource Centre: http://www.who.int/mental_health/mhgap/evidence/en/

PRACTICAL PRINCIPLES FOR ANTIPSYCHOTIC USE

The term psychosis refers to a nonspecific syndrome characterized by delusions (strong beliefs in ideas that are false and have no basis in reality), hallucinations (false sensory perceptions, commonly auditory, e.g. hearing voices not shared by others), loss of contact with reality and bizarre behaviour. This syndrome can result from a wide range of conditions, including both primary psychiatric disorders (schizophrenia and schizophrenia-related disorders), medical disorders (physical trauma, temporal lobe epilepsy, dementia, neurological and endocrine disease, metabolic abnormalities) and substance abuse (particularly of amphetamines and hallucinogens). Schizophrenia is a severe disorder and the most common primary psychosis. It typically begins in late adolescence or early adulthood and is characterized by fundamental distortions in thinking and perception and by inappropriate emotions. The disturbance involves the most basic functions that give the normal person a feeling of individuality, uniqueness and self-direction. Behaviour may be seriously disturbed during some phases of the disorder, leading to adverse social consequences. Individuals with schizophrenia are usually well oriented to person, place and time.

Early intervention for schizophrenia is essential, since there is a relationship between the duration of untreated psychosis and long-term outcome. The management of schizophrenia includes psychosocial intervention, which enhances functioning in areas such as independent living, relationships and work. Specific interventions are: family psychoeducation, supported employment, training in social skills and illness management skills, cognitive behavioural therapy and integrated treatment for comorbid substance abuse.

Antipsychotic agents are the primary medication for schizophrenia and related psychotic disorders. They are particularly effective against psychotic symptoms, while they have only modest, if any, impact on residual symptoms (lack of interest and initiative, blunted affect).

Before antipsychotic therapy is started, checking the patient's weight and blood pressure is generally recommended. Other suggested monitoring includes electrocardiogram (mandatory in some countries for specific antipsychotics, for example haloperidol), full blood count, urea and electrolytes, creatinine phosphokinase, liver function, blood glucose, lipid pattern and prolactin. If these laboratory examinations are not feasible, health-care providers should ask the patient and/or family member about the existence of cardiovascular, renal or hepatic abnormalities and whether drug treatments for these medical conditions have been prescribed and taken.

In clinical practice antipsychotic agents are classified into conventional or first-generation antipsychotics and atypical or second-generation antipsychotics. First-generation antipsychotics are further classified into phenothiazines (chlorpromazine, levomepromazine, promazine, periciazine, pipotiazine, fluphenazine, perphenazine, prochlorperazine and trifluoperazine), butyrophenones (benperidol and haloperidol), diphenylbutylpiperidines (pimozide), thioxanthenes (flupentixol and zuclopenthixol) and the substituted benzamides (sulpiride). Second-generation antipsychotics include amisulpride, aripiprazole, clozapine, olanzapine, paliperidone, risperidone, quetiapine, sertindole, ziprasidone, zotepine. First- and second-generation antipsychotics are similarly effective in the acute treatment of psychotic symptoms. However, the two groups of agents markedly differ in terms of adverse effects.

Box 50. mhGAP evidence-based recommendation: second-generation antipsychotic medications for psychotic disorders[1]

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.

[1]Source: WHO mhGAP Evidence Resource Centre: http://www.who.int/mental_health/mhgap/evidence/en/

According to the WHO EML, essential medicines for psychotic disorders are chlorpromazine, fluphenazine decanoate or enantate, haloperidol, risperidone and clozapine (complementary list, meaning that specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed). First-generation antipsychotics are indicated as an example of the class for which there is the best evidence for effectiveness and safety. Thus chlorpromazine represents phenothiazines; fluphenazine represents injectable long-acting antipsychotics; haloperidol represents butyrophenones. This does not apply for risperidone.

For patients with acute-phase schizophrenia or other primary psychotic disorders, health-care providers should consider the prescription of an oral antipsychotic. If more than one antipsychotic is available, the most suitable agent for each patient should be chosen on the basis of the following considerations:

- **Inclusion in the WHO EML.** This list includes the most efficacious, safe and cost-effective medicines.
- **Past history of antipsychotic responsiveness.** If a patient has already responded well to a specific agent, without intolerable side-effects, that agent might be chosen; if a patient failed to respond to a specific agent, or had intolerable side-effects, that agent should generally not be prescribed again.
- **Treatment adherence.** If treatment adherence is a problem, long-acting preparations, such as fluphenazine decanoate, should be considered.
- **Medical comorbidities.** If a patient suffers from specific medical problems, some agents should be avoided (e.g. thioridazine should be avoided in elderly patients with electrocardiogram abnormalities; olanzapine and clozapine should be prescribed with caution to patients with glucose abnormalities).
- **Subjective impact of adverse reactions.** Health-care providers should discuss with the patient and/or family member the subjective impact of side-effects (e.g. the relevance of weight gain may vary between males and females and in different age groups or cultures).
- **Costs.** Costs may vary according to the health-care system in which antipsychotics are prescribed.
- **New/old agents.** As a general rule, it is wise to prescribe established medicines, since the side-effect profile of new medicines becomes clear only after years of use.

Box 51. mhGAP evidence-based recommendation: antipsychotic medications for psychotic disorders[1]

Haloperidol or chlorpromazine should be routinely offered to individuals with psychotic disorders (including schizophrenia). Second-generation antipsychotics (except 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.

[1]Source: WHO mhGAP Evidence Resource Centre: http://www.who.int/mental_health/mhgap/evidence/en/

Treatment should be regularly monitored and its effect assessed after 6–8 weeks. If no improvement is seen after 8 weeks, the health-care provider may discuss with the patient and/or family member the possibility of switching to another oral antipsychotic. If treatment adherence is a major problem, the possibility of switching to a long-acting preparation may be discussed with the patient and/or family member. If adverse reactions are a major problem, the possibility of reducing the dose may be discussed; if they persist despite a dose reduction, a switch to another antipsychotic may be considered.

Box 52. mhGAP evidence-based recommendation: role of depot antipsychotic medication in patients requiring long-term antipsychotic treatment for psychotic disorders[1]

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.

[1]Source: WHO mhGAP Evidence Resource Centre: http://www.who.int/mental_health/mhgap/evidence/en/

It is generally suggested that treatment be started with low doses, increasing gradually. The minimum effective dosage should be prescribed. High doses of antipsychotics increase the risk of adverse reactions without providing additional benefit.

Box 53. mhGAP evidence-based recommendation: antipsychotic medications for psychotic disorders[1]

In individuals with psychotic disorders (including schizophrenia), the minimal effective dose of antipsychotics should be used, with the aim of minimizing adverse effects.

[1]Source: WHO mhGAP Evidence Resource Centre: http://www.who.int/mental_health/mhgap/evidence/en/

Health-care providers should not consider clozapine as first-line pharmacological treatment: it may cause life-threatening adverse effects, of which agranulocytosis is the best known.

During antipsychotic treatment, health-care providers should check for the development of neurological side-effects, including muscular rigidity, tremor, muscular spasm, abnormal involuntary movements of tongue, mouth and face. They should also check patients' body weight and blood pressure. Other suggested monitoring includes electrocardiogram (mandatory in some countries for specific antipsychotics, for example haloperidol), full blood count, urea and electrolytes, creatinine phosphokinase, liver function, blood glucose, lipid pattern and prolactin. If these laboratory tests are not feasible, the health-care provider should make regular medical examinations and note recent medical history, which may help in the recognition of symptoms suggesting the development of cardiovascular, renal or hepatic abnormalities.

After the acute episode has resolved, it is generally suggested that treatment be continued for at least one year. Without treatment, two thirds of patients relapse within one year.

Box 54. mhGAP evidence-based recommendation: duration of antipsychotic treatment in individuals with a first psychotic episode[1]

In individuals with a first psychotic episode, antipsychotic treatment should be continued for at least 12 months after the beginning of full and sustained remission. Any further continuation of antipsychotic drug treatment should be based on clinical review, preferably by a mental health specialist, in consultation with the family and taking into account the preferences of the individual.

[1]Source: WHO mhGAP Evidence Resource Centre: http://www.who.int/mental_health/mhgap/evidence/en/

Clozapine is generally reserved for patients without satisfactory clinical improvement despite the use of adequate doses, for adequate duration, of at least two antipsychotics (refractory schizophrenia). Before clozapine is used, antipsychotics of different classes are generally prescribed. In clozapine users, treatment effectiveness should be assessed over 6 months. In many countries, obligatory monitoring includes full blood count weekly for 18 weeks, at least every 2 weeks for the next year, and monthly thereafter. If these regular checks are not feasible, clozapine should not be prescribed.

Box 55. mhGAP evidence-based recommendation: antipsychotic medications for psychotic disorders[1]

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 non-specialist health-care providers, preferably under the supervision of mental health professionals and only if routine laboratory monitoring is available.

[1]Source: WHO mhGAP Evidence Resource Centre: http://www.who.int/mental_health/mhgap/evidence/en/

It is generally suggested one antipsychotic be used at a time. The concurrent use of two or more antipsychotics does not provide additional benefit but gives rise to additional adverse reactions and may interfere with treatment adherence.

Box 56. mhGAP evidence-based recommendation: combination of two or more antipsychotic medications for psychotic disorders[1]

For individuals with psychoses (including schizophrenia) who do not respond to adequate dose and duration of more than one antipsychotic medicine (using one medicine at a time), antipsychotic combination treatment may be considered by primary health-care professionals, preferably under the supervision of mental health professionals, with close clinical monitoring.

[1]Source: WHO mhGAP Evidence Resource Centre: http://www.who.int/mental_health/mhgap/evidence/en/

A switch from one antipsychotic to another should be undertaken with caution. Health-care providers should gradually reduce the dose of the first antipsychotic while gradually increasing the dose of the new agent.

Box 57. mhGAP evidence-based recommendation: antipsychotic medications for psychotic disorders[1]

In women with psychotic disorders (including schizophrenia) who are planning a pregnancy or are pregnant or breastfeeding, low-dose oral haloperidol or chlorpromazine may be considered.

[1]Source: WHO mhGAP Evidence Resource Centre: http://www.who.int/mental_health/mhgap/evidence/en/

PRACTICAL PRINCIPLES FOR MOOD STABILIZER USE

Bipolar disorder (or bipolar affective disorder or manic depressive illness) is a mental disorder characterized by episodes of both mania and major depression (bipolar depression).

A manic episode is characterized by a persistent elevation of mood, increased energy and activity, and usually marked feelings of well-being and both physical and mental efficiency. Mood is elevated out of keeping with the patient's circumstances and may vary from carefree joviality to almost uncontrollable excitement. Increased sociability, talkativeness, sexual energy and over-familiarity are often present, with a reduced need for sleep. Irritability, conceit and boorish behaviour may take the place of the more usual euphoric sociability. In severe manic episodes, attention cannot be sustained, and there is often marked distractibility. Self-esteem is often inflated, with grandiose ideas and overconfidence. Loss of normal social inhibitions may result in behaviour that is reckless, foolhardy, inappropriate to the circumstances and out of character. In very severe cases, delusions (usually grandiose) or hallucinations

(usually of voices speaking directly to the patient) are present, or the excitement, excessive motor activity and flight of ideas are so extreme that the subject is incomprehensible or inaccessible to ordinary communication. The onset of manic symptoms may be gradual, with weeks or months elapsing before the disorder becomes full-blown.

According to the WHO EML, essential medicines for bipolar disorders are carbamazepine, lithium and valproic acid.

In patients with severe manic episodes or marked behavioural disturbances as part of the syndrome of mania, health-care providers should consider a prescription of an antipsychotic; antipsychotics are rapidly effective in mania and are therefore considered antimanic agents. Lithium and valproate have also been shown to be effective in the acute treatment of mania. It should be noted that the onset of action of lithium is slower than that of antipsychotics or valproate.

Box 58. mhGAP evidence-based recommendation: antipsychotics and mood stabilizers in individuals with bipolar mania[1]

Haloperidol is recommended in individuals with bipolar mania. Second-generation antipsychotics may be considered as an alternative to haloperidol in individuals with bipolar mania if availability can be assured and cost is not a constraint.

Lithium, valproate or carbamazepine should be offered to individuals with bipolar mania. However, treatment with lithium should be initiated only in those settings where personnel and facilities for close clinical and laboratory monitoring are available.

[1]Source: WHO mhGAP Evidence Resource Centre: http://www.who.int/mental_health/mhgap/evidence/en/

In agitated, overactive patients, health-care providers may consider adjunctive short-term treatment with a benzodiazepine, such as diazepam.

Before antipsychotic therapy is started, checking the patient's weight and blood pressure is generally recommended. Other suggested monitoring includes electrocardiogram (mandatory in some countries for specific antipsychotics, for example haloperidol), full blood count, urea and electrolytes, renal function, liver function, blood glucose, lipid pattern and prolactin. If these laboratory examinations are not feasible, health-care providers should ask the patient and/or family member about the existence of cardiovascular, renal or hepatic abnormalities and whether drug treatments for these conditions have been prescribed and taken.

Suggested monitoring before the start of lithium therapy includes: renal function, thyroid function, electrocardiogram, full blood count, pregnancy test. If these laboratory examinations, and monitoring of lithium blood levels, are not feasible, lithium should not be prescribed. Health-care providers may choose to prescribe an antipsychotic.

Before valproate therapy is started, suggested monitoring includes: renal and hepatic function, full blood count, pregnancy test. If these laboratory examinations are not feasible, health-care providers should ask the patient and/or family member about the existence of cardiovascular, renal or hepatic abnormalities and whether drug treatments for these conditions have been prescribed and taken.

Treatment should be regularly monitored, and its effect should be assessed after 3 and 6 weeks. If no improvement is seen after 6 weeks, health-care providers may discuss with the patient and/or family member the possibility of augmenting treatment in combination strategies: antipsychotic plus lithium or antipsychotic plus valproate. If adverse reactions are a major problem, the possibility of reducing the dose may be discussed; if they persist despite a dose reduction, a switch to another mood stabilizer may be considered.

For prompt control of acute manic episodes with psychotic symptoms, health-care providers should consider intramuscular treatment only if oral treatment is not feasible. According to the WHO EML, essential medicines are chlorpromazine injection (e.g. 25 mg IM) or haloperidol injection (e.g. 5 mg IM). After intramuscular administration of an antipsychotic, health-care providers should monitor blood pressure, pulse, body temperature and respiratory rate; ECG monitoring is also recommended.

Box 59. mhGAP evidence-based recommendation: antidepressant medicines in individuals with a depressive episode in bipolar disorder[1]

Antidepressant medicines, always in combination with a mood stabilizer (lithium or valproate), may be considered for the treatment of moderate or severe depressive episodes of bipolar disorder. Selective serotonin-reuptake inhibitors (fluoxetine) should be preferred to tricyclic antidepressants.

Antidepressant treatment should begin at a low dose and be increased gradually if necessary.

Individuals should be monitored carefully for early symptoms or signs of mania. Antidepressant medication should be stopped soon after remission of depressive symptoms, while mood stabilizer should be continued.

[1]Source: WHO mhGAP Evidence Resource Centre: http://www.who.int/mental_health/mhgap/evidence/en/

Bipolar depression generally responds to antidepressants. However, health-care providers should consider that antidepressants, especially tricyclics, may induce a switch from depression to mania. Antidepressants appear less likely to induce mania when added to lithium, valproate or antipsychotic therapy. If an antidepressant is prescribed, a mood stabilizer should be given concurrently.

Lithium is regarded as the medicine of choice in the long-term maintenance phase of bipolar disorder, and health-care providers may consider lithium as initial monotherapy. Lithium monotherapy is probably effective against both manic and depressive relapse, although it is more effective in preventing

mania. Health-care providers should be aware that lithium has a narrow therapeutic index and blood levels must be monitored. Severe toxic effects can occur if renal excretion is impaired. During lithium treatment, thyroid function should be checked every 6 months. If monitoring of blood levels is not feasible, and in situations where supply of the drug may be frequently interrupted, lithium should not be prescribed.

If lithium is ineffective or poorly tolerated, or if lithium therapy is not feasible, treatment with valproate should be considered. Suggested monitoring during valproate treatment includes hepatic function, full blood count and pregnancy test. If these laboratory tests are not feasible, health-care providers should undertake regular medical examination, including taking recent medical history, which may help in the recognition of symptoms suggesting the development of blood or hepatic abnormalities.

Box 60. mhGAP evidence-based recommendation: antipsychotics and mood stabilizers (lithium, valproate or carbamazepine) for maintenance treatment of bipolar disorder[1]

Lithium or valproate or certain second-generation antipsychotics (aripiprazole, olanzapine, extended-release paliperidone, quetiapine, and long-acting risperidone injection) can be offered for 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 the supervision of a specialist.

[1]Source: WHO mhGAP Evidence Resource Centre: http://www.who.int/mental_health/mhgap/evidence/en/

If lithium and valproate are ineffective or poorly tolerated, or if therapy with one of these agents is not feasible, use of carbamazepine may be considered. Suggested monitoring before and during carbamazepine therapy includes: full blood count, liver and renal function, pregnancy test. If these laboratory tests are not feasible, health-care providers should undertake regular medical examination, including taking a recent medical history, which may help in the recognition of symptoms suggesting the development of blood or renal or hepatic abnormalities.

Long-term treatment should generally continue for at least 2 years after an episode of bipolar disorder. However, in patients with risk-factors for relapse, such as history of frequent relapses or severe manic episodes with psychotic symptoms, treatment may be prolonged for up to 5 years.

If possible, health-care providers should not prescribe lithium during pregnancy. Given in the first trimester of pregnancy, lithium increases the incidence of birth defects, specifically Ebstein anomaly. Administration during the final months of pregnancy can result in babies being lithium-toxic at birth. Similarly, although the teratogenicity of carbamazepine and valproic acid is not entirely clear, use of these agents in pregnancy should be avoided: both are associated with an increased risk of fetal abnor-

malities, particularly spina bifida. Valproic acid may be more dangerous than carbamazepine. If absolutely indicated, the use of low doses of haloperidol may be considered after discussion with the patient and/or family member. Haloperidol is excreted into breast milk.

Box 61. mhGAP evidence-based recommendation: antipsychotics and mood stabilizers in women with bipolar mania who are planning a pregnancy or are pregnant or breastfeeding[1]

In women with bipolar mania who are planning a pregnancy or are pregnant or breastfeeding, lithium and valproate should be avoided. In this group, low-dose haloperidol should be considered with caution.

[1]Source: WHO mhGAP Evidence Resource Centre: http://www.who.int/mental_health/mhgap/evidence/en/

PRACTICAL PRINCIPLES FOR BENZODIAZEPINE USE

Anxiety is a condition characterized by the subjective and physiological manifestations of fear. In anxiety disorders, individuals experience apprehension, but, in contrast to true fear, the source of the danger is unknown. The physiological manifestations of fear include sweating, shakiness, dizziness, palpitations, mydriasis, tachycardia, tremor, gastrointestinal disturbances, diarrhoea, and urinary urgency and frequency. If anxiety is generalized and persistent over months but not restricted to any particular environmental circumstances, the term generalized anxiety disorder is normally used. The dominant symptoms are variable but include complaints of persistent nervousness, trembling, muscular tension, sweating, light-headedness, palpitations, dizziness and epigastric discomfort. Fears that the patient or a relative will shortly become ill or have an accident are often expressed. Major depression occurs in almost two thirds of patients with generalized anxiety disorder, panic disorder in a quarter and alcohol abuse in more than one third.

Insomnia – disturbance of normal sleep patterns, with adverse daytime consequences – affects up to 50% of all adults at some point in life. The prevalence of insomnia seems to be higher in women and in later life. Individuals with insomnia report difficulty in falling or remaining asleep and usually fail to feel restored by sleep.

Generalized anxiety and sleep disorders may be the consequence of medical conditions, psychiatric conditions (mood or anxiety disorders), concomitant medicine treatments or medicine withdrawal, substance abuse (caffeine, nicotine, alcohol), stress and bad habits.

In evaluating patients with anxiety and/or sleep disorders, health-care providers should initially consider possible underlying medical causes, including hyperthyroidism and other endocrine illnesses, cardiac problems and other organ system dysfunctions. Medicine use (caffeine, cocaine) and medicine or substance withdrawal (alcohol, opiates, benzodiazepines) can cause anxiety and insomnia. If a medical disorder or medicine use or withdrawal is a plausible reason for anxiety, the underlying cause should be

treated or removed. If none of these is a plausible reason for anxiety or insomnia, health-care providers might investigate whether major depression or other psychiatric disorder is present. If there is another psychiatric disorder, that disorder should be treated first. For individuals with sleep disorders, if no psychiatric comorbidities are present, health-care providers may suggest behavioural interventions, such as going to bed at the same time, reserving bed for sleep, reducing caffeine intake and avoiding strenuous exercise or mental activities near bedtime. In individuals with anxiety disorders, if no psychiatric comorbidities are present, health-care providers may explain to the patient that chest pain, indigestion, sweating and sexual dysfunction are symptoms of anxiety.

Non-pharmacological treatment strategies should be considered first: empathic listening, reassurance and guidance should always be offered.

Benzodiazepines are structurally-related compounds that reduce anxiety when given at low doses and induce sleep at higher doses. Clinical guidelines generally recommend that benzodiazepines be prescribed to treat anxiety or insomnia that is severe, disabling and causing extreme distress. Health-care providers should be aware that benzodiazepine use is associated with dependence liability and withdrawal symptoms, and benzodiazepines should therefore be used at the lowest effective dose for the shortest possible period of time (maximum 4 weeks).

Use of benzodiazepines is under international control. These agents are internationally regulated by the Convention on Psychotropic Substances, 1971 (United Nations). Health-care providers should be aware that benzodiazepine use may also be under national control and must comply with all national, regional and local regulations.

Benzodiazepines can be grouped, according to their elimination half-life, into short/intermediate and long half-life agents. Short/intermediate half-life agents include alprazolam (intermediate), lorazepam (short), oxazepam (short), temazepam (intermediate) and triazolam (ultra-short); long half-life agents include diazepam, chlordiazepoxide, flurazepam and nitrazepam. Benzodiazepines with short elimination half-life are preferred to minimize daytime sedation but cause rebound symptoms more often than agents with longer elimination half-life. Ultra-short half-life benzodiazepines are generally not recommended because of the possibility of rebound symptoms.

Benzodiazepines hasten the onset of sleep, increase total sleeping time and reduce nocturnal awakenings, pathological anxiety, agitation and tension.

According to the WHO EML, the essential medicine for anxiety and sleep disorders is diazepam. Diazepam is indicated as an example of the class for which there is the best evidence for effectiveness and safety and represents benzodiazepines.

In the pharmacological treatment of severe and disabling insomnia, a benzodiazepine may be considered for only a short period of time (maximum 4 weeks).

In individuals with generalized anxiety disorder, health-care providers may consider using a benzodiazepine for a limited period only. The main objective may be to reduce symptoms sufficiently to allow the patient to engage in treatments based on cognitive behavioural techniques. A short course (maximum

4 weeks) at the lowest possible dose for a predefined duration of treatment may be used for initial management. Diazepam may be indicated when an anxiolytic effect is needed during the day and a hypnotic effect at night.

Benzodiazepine use should not be continued beyond 4 weeks, as chronic use may lead to dependence and withdrawal symptoms. Duration of therapy should be discussed with the patient, and a follow-up visit should be scheduled in advance (by office visit if possible, otherwise by telephone or other means) to re-evaluate anxiety and sleep patterns. Health-care providers should be aware that risk factors for dependence include high dosage, continuous use, use of short half-life benzodiazepines, and use in addiction-prone individuals and those with a history of medicine or alcohol dependence.

Since major depression often complicates anxiety symptoms, health-care providers should consider the use of antidepressants. Some tricyclic antidepressants (imipramine, clomipramine) and SSRIs have been shown to be effective for treating patients with generalized anxiety alone or in association with depression. Antidepressants may be prescribed at low doses initially, and treatment may then be up-titrated to the normal antidepressant dosage. Treatment response should be assessed after 6 weeks. Health-care providers should taper benzodiazepine doses gradually. If anxiety symptoms are still present, a trial with an antidepressant may be considered. Antidepressants usually take weeks to relieve symptoms and, after remission is achieved, treatment should be prolonged for up to 6–8 months to prevent relapse.

Abrupt benzodiazepine withdrawal can cause a syndrome characterized by anxiety, depression, impaired concentration, insomnia, headache, dizziness, tinnitus, loss of appetite, tremor, perspiration, irritability, perceptual disturbances such as hypersensitivity to physical, visual and auditory stimuli, abnormal taste, nausea, vomiting, abdominal cramps, palpitations, mild systolic hypertension, tachycardia and orthostatic hypotension.

Health-care providers should use benzodiazepines with care in elderly or debilitated patients who may be more prone to adverse effects.

Benzodiazepines should be avoided during pregnancy. Health-care providers should advise women of child-bearing age to discontinue benzodiazepines if they intend to become, or suspect that they are, pregnant. Use during the first trimester has been associated with congenital malformations and use in the third trimester may be associated with neonatal withdrawal symptoms (floppy infant syndrome). Benzodiazepines should not be given to lactating mothers.

Further details on appropriate use of medicines for mental disorders can be found in the WHO mhGAP Evidence Resource Centre: http://www.who.int/mental_health/mhgap/evidence/en/

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IMPROVING ACCESS TO AND APPROPRIATE USE OF MEDICINES FOR MENTAL DISORDERS

Access to essential medicines for mental disorders at all levels of the health system remains a particular challenge in many low- and middle-income countries. Access to medicines for mental disorders (or psychotropic medicines) encompasses rational selection, availability, affordability and appropriate use of those medicines. This report, based on a consultative process and extensive literature reviews, provides information to improve access to essential medicines for mental disorders. It examines current barriers to access to psychotropic medicines and identifies key actions for overcoming those barriers, organized as a function of four access components – selection, availability, affordability, appropriate use – and across four health-care levels, in a 4 x 4 access framework. Further, it provides evidence-based guidance for appropriate use of medicines in people with mental disorders.

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