Pharmacological treatment of mental disorders in primary health care

World Health Organization

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Table of Contents

Acknowledgements

The World Health Organization (WHO) definition of rational use of medicines, formulated in 1985, emphasizes that patients need to "receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community" (World Health Organization, 1985). According to this definition irrational use of medicines may refer to lack of access to essential medications or to inappropriate use of medications that are accessible and available.

According to *The World Health Report 2001,* access to essential medications is a priority. Essential psychotropic drugs should be provided and made constantly available at all levels of health care. These medicines should be included in every country's essential drugs list, and made available whenever possible. In some countries, this may require enabling legislation changes. These drugs can ameliorate symptoms, reduce disability, shorten the course of many disorders, and prevent relapse. They often provide the first-line treatment, especially in situations where psychosocial interventions and highly skilled professionals are unavailable.

In addition to access, appropriate use of medicines for mental disorders should be improved. Use of medicines for mental disorders is influenced by several factors, including lack of adequate knowledge about prescription and use, economic influences, cultural factors, community beliefs, poor communication between prescribers and patients, and poor adherence to correctly prescribed medicines. Consequently, strategies to promote more appropriate use of medicines need to involve those who prescribe medicines (physicians, nurses, other health care providers), those who dispense medicines (community and hospital pharmacists) and those who use medicines or supervise its proper intake (patients, care givers, family members) (World Health Organization, 2005).

During the last 20 years evidence-based treatment guidelines have been developed and regularly updated in many countries by national committees, scientific societies and other organizations. These guidelines consist of systematically developed statements to help prescribers make decisions about appropriate treatments for specific clinical conditions. Whenever possible, statements are evidence-based, that is, are based on systematic analyses of data from randomised clinical trials, systematic reviews and meta-analyses. Developing and maintaining evidence-based treatment guidelines is an exercise that requires time and resources, and this may not be feasible in low- and middle-income countries (LAMIC). Yet, LAMIC cannot directly apply and use guidelines that were developed for use in other countries with systems that are often much better resourced.

The present manual attempts to provide simple, adequate and evidence-based information to health care professionals especially in low- and middle-income countries to be able to provide pharmacological treatment to persons with mental disorders. It is hoped that use of this manual will enhance the knowledge and competence of those health professionals who are at the forefront of health care delivery in resource poor health systems. This will facilitate much needed scaling-up services for person with mental, neurological and substance use disorders envisaged in mental health Gap Action Programme of the World Health Organization.

Benedetto Saraceno

1.1 Mental disorders are estimated to account for 12% of the global burden of disease, but only a minority of persons affected receive basic treatment. Whereas there is evidence from industrialized countries that not all people with mental disorders receive adequate treatment, in developing countries mental health services are totally lacking and large segments of the population do not have ready access to health facilities, which tend to be based in hospitals and oriented predominantly towards urban conditions. In an attempt to strengthen the health care system and achieve low-cost but effective and efficient health services, attention is being increasingly focused on the development of a primary health care strategy. Moreover, it has been repeatedly shown that much of psychiatric morbidity is seen at the primary care level. For these reasons the role of primary health care providers becomes crucial for the delivery of effective and widespread mental health care.

1.2 The World Health Organization (WHO) reviewed evidence for effective treatment of mental disorders, and concluded that a combined psychosocial and pharmacological approach is likely to yield the best results.

1.3 This manual is a reference source to assist physicians working in the primary health care through increasing their knowledge and improving their routine clinical practice in using medicines for mental disorders. However, in the primary health care not all countries can afford to have all patients treated by a medical doctor. In many of the developing countries over 80% of outpatient consultations are done by medical assistants, clinical officers, nurses and village health workers operating from district hospitals, health centres and dispensaries. Consequently, this manual aims to additionally benefit other health care professionals including specialist physicians (internal medicine specialists, gynaecologists, cardiologists and others) and non-doctor primary health care professionals (nurses, social workers, occupational therapists) who might be involved in care of persons with mental disorders. The term health care professional is used throughout this manual to identify all these professional categories. Prescription and use of psychotropic medicines is often controlled by national laws and regulations; these need to be followed by all health care professionals.

1.4 As specified in the title, this manual is a reference source about pharmacological treatments only, and does not cover the overall management of mental disorders that includes a variety of non-pharmacological and service-organization interventions.

1.5 This manual is primarily intended to cover the use medicines for mental disorders in adults. However, relevant information on the use of medicines in specific age groups or populations, such as children and adolescents, elderly, pregnant and breast feeding women, and people with physical disorders, are included in each chapter.

1.6 After a brief introduction discussing the concept and role of essential medicines in mental disorders, a chapter provides information on a few basic principles of rational prescribing. Five chapters concisely provide practical insights on how to effectively manage the psychopharmacological treatment of psychotic disorders, depressive disorders, bipolar disorders, generalized anxiety and sleep disorders, obsessive-compulsive disorders and panic attacks. An additional chapter provides information on the management of alcohol and opioid dependence. In order to better inform clinical practice, mental disorders are described in terms of clinical presentations rather than diagnostic categories. In each chapter, clinical presentations are described using the International Classification of Diseases - 10th Revision (ICD-10) as reference source document.

1.7 Considering that differences between countries or regions in the epidemiology of some disorders may be expected, and considering that differences between countries or regions in local organizations of health care services may additionally be present, it is anticipated that some conditions covered in this text may not be clinical priorities in the primary health care of all countries or regions.

1.8 Although this manual is directed to health care providers in primary health care, reference, supervision and support from specialist mental health professionals, whenever possible, should always be considered an essential component of any treatment plan.

1.9 This manual is based on a meta-review of all available systematic reviews of the evidence. This method is not as intensive as a primary systematic review of a specific intervention for a defined clinical disorder, but it has been used to provide a useful overview of large clinical areas, reducing the risk of selective citation and being of help in detecting publication bias. The main results of systematic reviews identified and selected through the review process were used to produce a set of treatment recommendations. Two reviewers were involved in this process (Corrado Barbui and Andreas Cipriani) and a third reviewer (Shekhar Saxena) helped solve any controversial issue. The quality of systematic reviews and the strength of each treatment recommendation was not rated using any standard grading system. Recommendations were subsequently sent to selected experts from all 6 WHO regions involving more than 20 countries. These experts were asked to check scientific accuracy and local applicability of the manual. A revised version of the manual was then drafted taking into consideration all comments and suggestions.

1.10 Material related to the development of this manual include: i) evidence retrieval, assessment and ii) synthesis and peer review process are available from WHO on request (email: mnh@who.int).

1.11 This manual is expected to be reviewed and updated every three years. Changes in recommendations, if any, before the regular updates will be available on the following WHO website- http://www.who.int/mental_health/management/treatment_disorders/en

Essential medicines for mental disorders

1.1 The World Health Report 2001 presents a variety of recommendations on how to improve care for people with mental disorders, including improving access to a limited selection of essential psychotropic medicines. These medicines should be made available at all levels of health care and should be included in the WHO Model List of Essential Medicines (EML), with health personnel trained to use them in treating people with mental disorders. Improving access to essential psychotropic medicines is a key component in strengthening access to effective mental health care services.

1.2 Essential psychotropic medicines are those that satisfy the priority mental health care needs of a population. They are selected with due regard to public health relevance, evidence of efficacy and safety, and comparative cost-effectiveness. They should be available within the context of functioning mental health delivery systems, at all times, in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford. Essential psychotropic medicines allow for the treatment of symptoms of mental disorders, shorten the course of many disorders, reduce disability and prevent relapse.

1.3 A large number of treatments are available for the pharmacological management of mental disorders. Many of these treatments have been shown to be effective in acute stages and in preventing relapses, but much remains unclear about their effectiveness in long-term treatment and in managing everyday mental disorders. Hence, not all "effective" drug therapies are "essential"; this may become clear once such factors as effectiveness of long-term applications, advantages over cheaper alternatives and cost-effectiveness are better understood.

1.4 In the WHO EML the following have been selected for the treatment and control of mental disorders: chlorpromazine, fluphenazine, haloperidol (medicines used in psychotic disorders); amitriptyline, fluoxetine (medicines used in depressive disorders); carbamazepine, lithium carbonate, valproic acid (medicines used in bipolar disorders); diazepam (medicines used in generalized anxiety and sleep disorders); clomipramine (medicines used in obsessive-compulsive disorders and panic attacks); methadone and buprenorphine (medicines used for substance dependence programmes (see box overleaf). It should be noted that chlorpromazine, fluphenazine, haloperidol, amitriptyline and diazepam 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

1

Essential medicines for mental disorders
(15th list, March 2007)

PSYCHOTIC DISORDERS:

Chlorpromazine
Injection	25 mg (hydrochloride)/ml.
Oral liquid	25 mg (hydrochloride)/5 ml.
Tablet	100 mg (hydrochloride).

Fluphenazine
Injection	25 mg (decanoate or enantate).

Haloperidol
Injection	5 mg.
Tablet	2 mg; 5 mg.

DEPRESSIVE DISORDERS:

Amitriptyline
Tablet	25 mg (hydrochloride).

Fluoxetine
Capsule or tablet	20 mg (present as hydrochloride).

BIPOLAR DISORDERS:

Carbamazepine
Tablet (scored)	100 mg; 200 mg.

Lithium carbonate
Capsule or tablet	300 mg.

Valproic acid
Tablet	200 mg; 500 mg (sodium valproate).

GENERALIZED ANXIETY AND SLEEP DISORDERS:

Diazepam
Tablet	2 mg; 5 mg.

OBSESSIVE-COMPULSIVE DISORDERS AND PANIC ATTACKS:

Clomipramine
Capsule	10 mg; 25 mg (hydrochloride).

MEDICINES USED IN SUBSTANCE DEPENDENCE PROGRAMMES:

Methadone
Concentrate for oral liquid	5 mg/ml; 10 mg/ml.
Oral liquid	5 mg/5 ml; 10 mg/5 ml.

Buprenorphine
Sublingual Tablets	2 mg; 8 mg.

The latest version of the WHO Model List of Essential Medicines can be found on the following website: http://www.who.int/medicines/publications/essentialmedicines/en/index.html

1

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.

1.5 Recent cost-effectiveness studies have concentrated on finding the relative advantages of newer classes of medicines over the older and more established ones. For example, newer antidepressants were compared to the older tricyclic antidepressants, and newer antipsychotics to the conventional ones. Findings indicated that while newer psychotropic medicines may have fewer or different side-effects, they are not significantly more effective, and they are usually more expensive.

1.6 Although this manual is built around essential psychotropic medicines, other medicines that are supported by scientific evidence of efficacy, and that may be of benefit for individuals with mental disorders, are similarly covered.

Basic principles of prescribing

1.1 The decision to prescribe a pharmacological treatment must take into consideration the potential risks and benefits to each individual patient. Health care providers should discuss with patients, family members and/or patients' carers these potential risks and benefits.

1.2 Health care providers should consider that medicines play an important role in the doctor-patient relationship, and should make an effort to enlist, recruit and involve the patient in a collaboration related to the prescribed medication. The psychological implications of receiving a drug therapy should be discussed and taken into account.

1.3 In general, health care providers and patients should consider that most psychiatric disorders can effectively be tackled by means 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 outcome. Consequently, health care providers should not passively consider medications as their only therapeutic strategy, and patients should not be given a message suggesting that modifications of thought, mood and conduct can be achieved by pharmacological means only. Articulated, comprehensive and individualized treatment plans may represent the best therapeutic option.

1.4 In general, prescriptions should not be issued before a detailed clinical assessment is completed, and before having explored the psychological mechanisms underlying symptoms.

1.5 It should be clear to the patient that the treatment is for a pre-planned period of time. This period may be related to the pharmacological properties of the drugs employed and/or to the condition under treatment.

1.6 Titration of most pharmacological treatments for mental disorders should be done gradually, especially in the elderly and in patients with concomitant medical illnesses. The minimum effective dose should be prescribed, based on an assessment both of how much of it is required to affect the target symptoms and of the patient's social, psychological and geographical situation, i.e., a patient from a rural area who must make an arduous journey to obtain treatment will require a larger supply than one with easier access to a pharmacy.

2

1.7 The dosages listed in this publication are mainly based on data available from western countries and health care providers prescribing psychotropic medicines for their patients in other parts of the world should be aware of inter-individual as well as ethnic differences in drug metabolism. Health care providers should always consult the national or local prescribing information or instructional material. The term "milligrams" has been abbreviated in mg throughout the text.

1.8 Patients should be informed of possible side-effects, and should also be informed about possible measures to manage them, i.e., reduction in the dose, reassurance that some of these side-effects are temporary.

1.9 Health care providers should be aware of all the substances, both medical and non-medical, being taken by the patient and the possible interactions. For example, alcohol and benzodiazepines should not be taken concurrently.

1.10 Health care providers should be aware that some pharmacological treatments for mental disorders are under international control. The use of medicines under international control is regulated by the Convention on Psychotropic Substances, 1971 (United Nations). In addition to international control, the use of some medicines may be under national control. Health care providers must be aware that international, national, regional and local drug regulations have to be strictly followed.

1.11 Health care providers should regularly monitor drug use, and should specifically ask how much of the medicine has been taken. It is commonplace that patient adherence to treatment varies.

1.12 In the choice of a specific medicine, health care providers should consider the availability and continuity of supply. In situations where continuity of supply of a medicine is likely to be interrupted, its use should be avoided.

1.13 Health care providers should be aware that a history of previous suicidal thoughts or attempts are important indications of possible suicidal behaviour. Such patients should be specifically asked about suicide and, if it is a possibility, health care providers must limit the amount of medicines prescribed and should also construct a regimen in which there is frequent clinical monitoring and also monitoring by family members and friends.

1.14 Health care providers should always take a history of substance abuse, including abuse of psychotropic medication. This information should be taken into consideration when considering the prescription of psychotropic medication.

1.15 Psychotropic drug discontinuation should be done gradually (25% of the dose per week).

1.16 In general, polypharmacy should be avoided. The term polypharmacy defines the concurrent use of two or more medicines belonging to the same pharmacological class (for example two or more antipsychotics or two or more antidepressants).

2

Medicines used in psychotic disorders

1.	Definition of psychotic disorders
2.	Preliminary assessment and initial management strategies
3.	Short-term treatment with antipsychotics
4.	Long-term treatment with antipsychotics
5.	Administration of antipsychotics
6.	Adverse reactions of antipsychotics
7.	Overdosage of antipsychotics
8.	Special patient populations
9.	Potentially relevant interactions
10.	Essential medicines for psychotic disorders

3

1. Definition of psychotic disorders

1.1 The term psychosis refers to a non-specific syndrome characterized by delusions (false beliefs), hallucinations (false sensory perceptions 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, neurologic and endocrine disease, metabolic abnormalities) and substance abuse disorders (particularly amphetamines and hallucinogens).

1.2 Schizophrenia is the most common primary psychosis. It is a severe disorder that typically begins in late adolescence or early adulthood; it is found approximately equally in men and women, though the onset tends to be later in women, who also tend to have a better course and outcome of this disorder. Epidemiological surveys report a point prevalence of 0.4%.

1.3 Schizophrenia 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. Delusions (strong belief in ideas that are false and without any

basis in reality), and hallucinations (commonly auditory hallucinations, e.g. hearing voices) are typical psychotic features of this disorder. Individuals with schizophrenia are usually well oriented to person, place and time.

1.4 Schizophrenia follows a variable course, with complete symptomatic and social recovery in about one-third of cases. Schizophrenia can, however, follow a chronic or recurrent course, with residual symptoms and incomplete social recovery. Individuals with chronic schizophrenia constituted a large proportion of all residents of mental institutions in the past, and still do where these institutions continue to exist. With modern advances in drug therapy and psychosocial care, almost half the individuals initially developing schizophrenia can expect a full and lasting recovery. Of the remainder, only about one-fifth continue to face serious limitations in their day-to-day activities. Even after the more obvious symptoms of this disorder have disappeared, some residual symptoms may remain. These include lack of interest and initiative in daily activities and work, social incompetence, and inability to take interest in pleasurable activities. These can cause continued disability and poor quality of life. These symptoms can place a considerable burden on families. It has been repeatedly demonstrated that schizophrenia follows a less severe course in developing countries.

1.5 Health care providers should consider the effect of culture and spirituality on the manifestation of psychiatric symptoms in the primary health care. Different cultures may express psychiatric symptoms in a metaphor or language that differs from the cultural background of the primary care professional and, where necessary and appropriate, interpreters may be used to elicit symptomatology. In addition, some experiences (e.g. hearing voices) may be normal in a culture, while resembling psychopathology. Care must be given to avoid misinterpretation.

2. Preliminary assessment and initial management strategies

2.1 Health care providers should initially exclude the possibility that an organic illness or a substance abuse disorder is the underlying cause of psychotic symptoms. A detailed medical and psychiatric history, physical and neurologic examination, and mental status assessment should be carried out.

2.2 In psychoses caused by medical conditions the underlying condition should be treated, with adjunctive psychiatric management for the behavioural problems. In psychoses caused by substance abuse, detoxification or adjustment of medication may be required.

2.3 In principle, acutely psychotic patients should be evaluated without delay, considering that agitation and uncooperativeness may be present. Health care providers should

engage the patient in a dialogue. Family members and friends may represent a valid aid in reducing the level of uncooperativeness.

2.4 Health care providers may obtain relevant clinical details from individuals who know the patient well. Changes in sleeping pattern, speech, behaviour, or daily routine should be investigated.

2.5 Health care providers should evaluate whether the patient is contemplating self injury. Suicide attempts may occur at any point in the illness, but the most worrisome periods are during the acute psychotic exacerbations, when a patient may respond to hallucinations or delusions, and during the weeks following an acute psychotic exacerbation, when a patient may experience post-psychotic depressive symptoms.

> *Patients with schizophrenia contemplating self injury should be intensively monitored; monitoring may include admission to an inpatient facility, close supervision by family members or by other individuals who know the patient well*

3

2.6 Early intervention for schizophrenia is essential, since there is a relationship between length of untreated psychosis and poor long-term outcome.

2.7 The management of schizophrenia includes psychosocial intervention. Psychosocial intervention enhances functioning in areas such as independent living, relationships and work. Specific interventions are: family psychoeducation, supported employment, social skill training, teaching illness management skills, cognitive-behavioural therapy and integrated treatment for comorbid substance abuse.

> *Patients with schizophrenia should be offered psychosocial intervention in addition to pharmacological intervention*

3. Short-term treatment with antipsychotics

3.1 The primary aim is to reduce the most serious symptoms, including hallucinations, delusions, agitation and disorganised thought and behaviour.

3.2 Antipsychotic agents are the primary medication for schizophrenia and related psychotic disorders. These agents are particularly effective against psychotic symptoms, while their impact on residual symptoms (lack of interest and initiative, blunted affect) is modest or absent.

3.3 Before starting antipsychotic therapy, it is generally recommended to check 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 tests, 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 therapies for these medical conditions have been prescribed and taken.

3.4 In clozapine users, before starting treatment, obligatory monitoring in many countries includes full blood count. If full blood count is not feasible, clozapine should not be prescribed.

3.5 In clinical practice antipsychotic agents are classified into conventional or first-generation antipsychotics and atypical or second-generation antipsychotics. First-generation antipsychotics are classified into phenothiazines (chlorpromazine, levomepromazine, promazine, pericyazine, pipotiazine, fluphenazine, perphenazine, prochlorperazine and trifluoperazine), butyrophenones (benperidol and haloperidol), diphenylbutylpiperidines (pimozide), thioxantenes (flupentixol and zuclopentixol) and the substituted benzamides (sulpiride). Second-generation antipsychotics include amisulpride, aripiprazole, clozapine, olanzapine, risperidone, quetiapine, sertindole, ziprasidone, zotepine.

3.6 With the exception of clozapine (which is more effective than first-generation antipsychotics in the pharmacological treatment of refractory schizophrenia), first- and second-generation antipsychotics are similarly effective in the acute treatment of psychotic symptoms. However, these two groups of agents markedly differ in terms of adverse effects (see 6.1 and 6.2 and 6.3).

3.7 According to the WHO EML, essential medicines for psychotic disorders are chlorpromazine, fluphenazine decanoate or enantate, haloperidol. These medicines 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.

3.8 In 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, health care providers should chose the most suitable agent for each patient taking into consideration the following aspects: 1) Inclusion in the WHO EML: this list includes the most efficacious, safe and cost-effective medicines; 2) Past history of antipsychotic responsiveness: if a patient has already responded well, without intolerable side-effects to a specific agent, that agent might be chosen; if a patient failed to respond, or had intolerable side-effects, to a specific agent, that agent should generally not be prescribed any more; 3) Treatment adherence: if treatment

adherence is a problem, physicians should consider long-acting preparations, such as fluphenazine decanoate; 4) 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 cautiously prescribed to patients with glucose abnormalities); 5) The subjective impact of adverse reactions: health care providers should discuss with the patient and/or family member the plausible impact of side-effects (e.g. the relevance of weight gain may vary between males and females and in different age groups or cultures); 6) Cost implications: these may change according to the health care system in which antipsychotics are prescribed; 7) New/old agent: as a general rule, it is wise to prescribe well known medicines, since the side-effect profile of new medicines becomes clear only after years of marketing.

> *Psychotic symptoms including delusions, hallucinations, bizarre behaviour, illogic ideas, thought blocking, deficiencies in speech, neologisms, incoherence and loose thought associations may be effectively treated with antipsychotic medicines*

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

> *Treatment effectiveness should be assessed after 6-8 weeks and, after the acute episode has resolved, health care providers should generally prolong treatment for at least one year*

3.10 Health care providers should not consider clozapine as first-line pharmacological treatment, as it may cause life-threatening adverse effects of which agranulocytosis is the best known (See 5.6 and 5.7).

3.11 For prompt control of acute 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 intramuscular) or haloperidol injection (e.g. 5 mg intramuscular). After intramuscular antipsychotic administration, health care providers should monitor blood pressure, pulse, body temperature and respiratory rate.

3.12 In addition to pharmacological and non-pharmacological interventions, health care providers should provide information to patients and family members, emphatic listening, reassurance and psychological support. This may help develop a good relationship and a therapeutic alliance that may positively influence the patient subjective well-being and the long-term outcome of the disorder.

3.13 During antipsychotic treatment, health care providers should check whether neurologic side-effects have developed, including muscular rigidity, tremor, muscular spasm, abnormal involuntary movements of tongue, mouth and face. Health care providers should additionally check 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 tests, blood glucose, lipid pattern and prolactin. If these laboratory tests are not feasible, health care providers should remember to regularly make a medical examination, including a recent medical history that may help recognize symptoms suggesting the development of cardiovascular, renal or hepatic abnormalities.

4. Long-term treatment with antipsychotics

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

4.2 There is no reliable strategy to identify the minimum effective dose to prevent relapse. During long-term treatment, health care providers may either maintain or moderately decrease the dose administered during the acute phase, according to clinical status and circumstances.

4.3 Treatment adherence may be a major problem in the long-term. In these cases, health care providers should discuss with the patient and/or family member the possibility to switch to a long-acting preparation. Non-pharmacological interventions to increase adherence (patient education, family psychoeducation, specific psychotherapeutic interventions) may additionally be implemented.

4.4 In clozapine users, obligatory monitoring in many countries includes weekly full blood count for 18 weeks, at least every 2 weeks for one year, and monthly thereafter. If these regular checks are not feasible, clozapine should not be prescribed.

5. Administration of antipsychotics

5.1 It is generally suggested to use one antipsychotic at a time. The concurrent use of two or more antipsychotics do not provide additional benefit, while it produces additional adverse reactions and may interfere with treatment adherence.

5.2 High doses of antipsychotics increase the risk of adverse reactions without providing additional benefit.

5.3 It is generally suggested to start with low doses, and to increase gradually. The minimum effective dosage should be prescribed.

5.4 Long-acting antipsychotics should be prescribed only if treatment adherence constitutes a serious problem. Usually a test dose of a long-acting preparation (e.g. 12.5 mg intramuscular of fluphenazine decanoate) is initially prescribed, then after 4-10 days the dosage is titrated to effective maintenance therapy (e.g. 12.5-50 mg intramuscular of fluphenazine decanoate every 2-4 weeks).

5.5 Switching from one antipsychotic to another should be performed with caution. Health care providers should gradually reduce the dose of the first antipsychotic while gradually increasing the dose of the new antipsychotic.

5.6 Clozapine is generally reserved for patients without satisfactory clinical improvement despite the use of adequate doses of at least two antipsychotics prescribed for adequate duration (refractory schizophrenia). Before using clozapine, antipsychotics of different classes are generally prescribed. In clozapine users, treatment effectiveness should be assessed over six months.

5.7 Prescribing clozapine without white blood cell monitoring may increase the risk of fatal agranulocytosis.

6. Adverse reactions of antipsychotics

6.1 Antipsychotic side-effects are generally grouped into neurologic and anticholinergic side-effects. Neurologic side-effects include parkinsonian effects (resting tremor, akinesia, rigidity), acute dystonias (slow, prolonged muscular spasms), akathisia (subjective feeling of agitation), neuroleptic malignant syndrome (fever, sweating, confusion, increased blood pressure and pulse, muscular rigidity, very high creatine phospokinase, renal failure), tardive dyskinesia (abnormal involuntary movements of tongue, head, face, mouth), and convulsions. Anticholinergic side-effects include peripheral effects (dry mouth, blurred vision, constipation, urinary retention) and central effects (severe agitation and confusion).

6.2 If patients develop parkinsonian effects, health care providers should reduce the dose of antipsychotic. If parkinsonian effects persist despite the dose decrease, health care providers may consider the prescription of antiparkinson agents, such as biperiden 2-4 mg/day.

6.3 Side-effects associated with the use of second-generation antipsychotics include hyperglycaemia, ketoacidosis, diabetes, and lipid dysregulation. Among second-generation antipsychotics, clozapine and olanzapine are associated with the greatest risk of clinically significant weight gain, diabetes mellitus and dyslipidaemia. Antipsychotic related metabolic abnormalities are worrisome, as they are risk factors for cardiovascular morbidity and mortality.

6.4 Other side-effects associated with antipsychotic use include weight gain, sedation, electrocardiogram abnormalities, orthostatic hypothension, increased prolactin resulting in gynecomastia, galactorrhea, amenorrhea, impotence, leukopenia, agranulocytosis, jaundice, elevated liver enzymes, photosensitivity, skin eruptions, retinal pigmentation.

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6.5 Clozapine can cause serious, life-threatening adverse effects of which agranulocytosis is the best known. Risk of fatal agranulocytosis is around ten times higher in clozapine than other antipsychotic users. This risk is managed by regular monitoring full blood count. It has also been suggested that clozapine is associated with myocarditis, cardiomyopathy and pulmunary embolism.

7. Overdosage of antipsychotics

7.1 The outcome of antipsychotic overdose is generally favourable unless other central nervous system depressants, such as alcohol and benzodiazepines, have been ingested. Overdosage of phenothiazines may cause more severe symptomatology than other antipsychotic classes.

7.2 Antipsychotic overdose is characterized by hypotension, tachycardia, hypothermia, arrhythmia, drowsiness, dystonias and seizures.

7.3 If antipsychotic overdosage of antipsychotics is suspected, referral to acute medical facility is recommended.

8. Special patient populations

8.1 In elderly patients with behavioural symptoms that may be associated with cognitive impairment or dementia antipsychotics should be prescribed with caution. In general, one half to one third the adult dose is recommended in the elderly, who may be more susceptible to parkinsonian and anticholinergic side-effects. Phenothiazines should be used with caution given the risk of hypotension, and thioridazine may not be considered a first-choice medicine if other antipsychotics are available. Haloperidol has been widely used in the elderly, although the risk of electrocardiogram changes should be monitored.

Fluphenazine

Starting dose: 2.5-10 mg/day orally.

Therapeutic dose: 10-20 mg/day orally.

Long-acting preparations for patients with low treatment adherence: Test dose 12.5 mg intramuscular, after 7 days 12.5-25 mg intramuscular every 3-4 weeks. Do not exceed 50 mg intramuscular every 3-4 weeks.

Common adverse effects: akathisia, dystonic extrapyramidal effects, parkinsonian extrapyramidal effects, tardive dyskinesia, tardive dystonia, dry mouth, blurred vision, constipation, urinary retention, nasal congestion, dizziness, drowsiness, orthostatic hypotension, photosensitivity.

Serious adverse effects: blood dyscrasias, agranulocytosis, leukocytopenia, thrombocytopenia, cholestatic jaundice, neuroleptic malignant syndrome, paralytic ileus, priapism, electrocardiogram changes, including QT prolongation and torsades de pointes, seizures, systemic lupus erythematosus-like syndrome, temperature regulation dysfunction.

WHO EML: long-acting injection 25 mg.

Haloperidol

Starting dose: 2-5 mg/day orally.

Therapeutic dose: 4-10 mg/day orally.

For prompt control of psychotic symptoms: 2 or 5 mg intramuscular, may be repeated after one hour if needed.

Long-acting preparations for patients with low treatment adherence: Test dose 25 mg intramuscular, after 7 days 50-150 mg intramuscular every 4 weeks.

Common adverse effects: akathisia, dystonic extrapyramidal effects, parkinsonian extrapyramidal effects, blurred vision, constipation, decreased sweating, dry mouth, nasal congestion, dizziness, drowsiness, orthostatic hypotension, photosensitivity.

Serious adverse effects: tardive dyskinesia, tardive dystonia, agranulocytosis, cholestatic jaundice, neuroleptic malignant syndrome, paralytic ileus, priapism, electrocardiogram changes, including QT prolongation and torsades de pointes, seizures, systemic lupus erythematosus-like syndrome, temperature regulation dysfunction.

WHO EML: tablet 2 mg, tablet 5 mg; injection 5 mg.

Medicines used in depressive disorders

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1. Definition of depressive disorders

1.1 Depression is a condition characterized by episodes of depressed mood. Each episode is characterized by lowering of mood, reduction of energy, and decrease in 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 the mild form, 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. Though depressive feelings are common, especially after experiencing setbacks in life, depressive disorder is diagnosed only when the symptoms reach a threshold and last at least two weeks. Depression needs to be distinguished from states of subjective distress and emotional disturbance, possibly

The following two questions may be used in patients who might be at risk for depression:
(1) "During the past 4 weeks have you often been bothered by feeling down, depressed or hopeless?"
(2) "During the past 4 weeks have you often been bothered by having little interest or pleasure in doing things?"

interfering with social functioning and performance, arising in the period of adaptation to a significant life change or a stressful life event (e.g. death of a loved one).

1.2 In some circumstances, symptoms of anxiety and depression are both present, but neither is clearly predominant, and neither type of symptom is present to the extent that justifies a diagnosis if considered separately. In these situation the term mixed anxiety and depressive disorder is generally used.

1.3 Depression is usually grouped into mild, moderate and severe. Mild to moderate depression is characterized by depressive symptoms and some functional impairment; severe depression is characterized by depressive symptoms, functional impairment, agitation or psychomotor retardation, and marked somatic complaints.

1.4 Depression is more common in women than in men. The average point prevalence of unipolar depressive episodes has been estimated to be 1.9% for men and 3.2% for women, and that 5.8% of men and 9.5% of women will experience a depressive episode in a 12-month period. These prevalence figures vary across populations. Depression can affect individuals at any stage of the life span, although the incidence is highest in middle age.

1.5 Depressive symptoms often markedly impair everyday functioning. Global burden of disease 2004 update analysis shows that unipolar depressive disorders place an enormous burden on society and are ranked as the third leading cause of burden among all diseases, accounting for 4.3% of the total disability-adjusted life years (DALYs). While these estimates clearly demonstrate the current very high level of burden resulting from depression, the outlook for the future is even starker. By the year 2030, if current trends for communicable disease control and demographic and epidemiological transition continue, the burden of depression will increase to 6.2% of the total burden of disease, becoming the leading cause of DALYs lost.

1.6 The term unipolar depression is sometimes used to make a distinction between depressive episodes in the course of major (or unipolar) depression and depressive episodes in the course of bipolar disorder (bipolar depression).

1.7 Depression is essentially an episodic recurring disorder, each episode lasting usually from a few months to a few years, with a normal period in between. In about 20% of cases, however, depression follows a chronic course with no remission, especially when adequate treatment is not available. The recurrence rate for those who recover from the first episode is around 35% within 2 years and about 60% at 12 years. The recurrence rate is higher in those who are more than 45 years of age. One of the particularly tragic outcomes of a depressive disorder is suicide.

1.8 Considering that it is unclear whether health care providers should routinely screen all patients seen in primary care for depression, it is generally recommended to screen only patients at risk (family or personal history of depression, multiple medical problems, unexplained physical symptoms, chronic pain, or use of medical services that is more frequent than expected) using very simple questions. A two-question case-finding instrument has been shown to be reliable in primary care. Only individuals with affirmative answers to both questions should be further investigated for depressive symptoms.

1.9 Depressive symptoms can be confused with those of other medical illnesses (i.e. weight loss and fatigue may be associated with diabetes, cancer, and thyroid disease). In addition, the use of some medicines is associated with depressive symptoms (benzodiazepines, beta-blockers, narcotics and steroids).

1.10 Depressive symptoms can also be confused with normal, subjective distress arising after exposure to extreme stressors (e.g. domestic violence, death of a loved one, disaster). Yet, such events are at the same time also risk factors for depressive disorders. If the subjective distress of the patient is in terms of intensity and persistence out of proportion of the patient's life situation, then depressive disorder is likely present.

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2. Preliminary assessment and initial management strategies

2.1 Health care providers should initially exclude the possibility that an organic illness or a substance abuse disorder is the underlying cause of depressive symptoms. A detailed medical and psychiatric history, physical and neurologic examination, and mental status assessment should be carried out.

2.2 Depressed patients may contemplate self-injury and suicide. Health care providers may use the patient's history and current behaviour to assess the risk. In addition, the following questions may help:

    (1)   "Do you ever think of hurting yourself or taking your own life?"

    (2)   *(if YES)*   "Do you currently have a plan?"

    (3)   *(if YES)*   "What is your plan?"

> *Patients with major depression contemplating self injury should be intensively monitored; monitoring may include admission to an inpatient facility, close supervision by family members or by other individuals who know the patient well*

2.3 Health care providers should not avoid these questions for fear of suggesting the idea of suicide. Even in the absence of immediate risk, physicians should emphasize to patients the importance of reporting suicidal thoughts, especially if they are becoming more intense or frequent.

3. Short-term treatment with antidepressants

3.1 Antidepressants are effective in around 60% of patients, although more than 30% of patients are placebo responders. Antidepressants may take up to 6-8 weeks to have a full therapeutic effect.

3.2 Antidepressants are classified into several classes according to the mechanism of action: tricyclic or related antidepressants (amitriptyline, clomipramine, desipramine, dothiepin, dosulepine, doxepin, imipramine, lofepramine, nortriptyline, trimipramine, mianserine, trazodone); monoamine oxidase inhibitors (moclobemide, isocarboxazid, phenelzine, tranylcypromine); selective serotonin reuptake inhibitors (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline); other antidepressants (duloxetine, mirtazapine, reboxetine, venlafaxine).

3.3 All antidepressants are similarly effective in the acute treatment of depressive symptoms. However, antidepressants differ in terms of adverse effects. The efficacy of antidepressants has been demonstrated in clinical trials conducted in patients with moderate to severe depression only. In contrast, the efficacy of antidepressants in mild depression is unproven.

3.4 Health care providers should offer information, empathetic listening, reassurance and psychological support (e.g. problem solving counselling) and referral to relevant social services and resources in the community. This may also help develop a good relationship and a therapeutic alliance that may positively influence the patient's subjective well-being. If feasible, plan a new visit after 2-4 weeks. In mild depression, health care providers may consider treatment with antidepressants if symptoms get worse or persist after 4 weeks of watchful waiting.

3.5 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. Thus amitriptyline represents tricyclic antidepressants.

3.6 In patients with moderate to severe symptoms, functional impairment, or a long duration of illness, health care providers should consider the prescription of an oral antidepressant. If more than one antidepressant is available, health care providers should choose the most suitable agent for each patient taking into consideration the following aspects: 1) Inclusion in the WHO EML: this list includes the most efficacious, safe and cost-effective medicines; 2) Past history of antidepressant responsiveness: if a patient has

> *Health care providers should consider treatment with antidepressants in individuals with moderate to severe major depression*

already responded well, without intolerable side-effects, to a specific agent, that agent might be chosen; if a patient failed to respond, or had intolerable side-effects, to a specific agent, that agent should generally not be prescribed any more; 3) 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 if regular electrocardiogram checks are not feasible; venlafaxine should be cautiously prescribed in patients with high blood pressure); 4) Plausible impact of adverse reactions: the subjective impact of side-effects should be taken into consideration (e.g. the relevance of sexual dysfunctions varies between males and females and in different age groups); 5) Cost implications: these may change according to the health care system in which antidepressants are prescribed; 6) New/old agent: as a general rule, it is wise to prescribe well known medicines, since the side-effect profile of new medicines becomes clear only after years of practice.

3.7 The use of monoamine oxidase inhibitors is generally not recommended in primary care due to risk of significant side-effects and no obvious therapeutic advantage as first-line medications.

3.8 While tricyclic antidepressants are toxic when taken in overdose, fluoxetine and other selective serotonin-reuptake inhibitors are less dangerous and may be prescribed in patients at risk of self-harm.

3.9 Assess treatment effectiveness after 6-8 weeks. If no improvement is seen after 8 weeks, discuss with the patient the possibility to increase the dose or to switch to another antidepressant (it is generally recommended to change medicine class if antidepressants of different classes are available). If treatment adherence is a major problem, discuss with the patient the possibility to switch to another antidepressant that may be better tolerated. If adverse reactions are a major problem, discuss with the patient the possibility to decrease the dose. If adverse reactions persist despite a dose reduction, a switch to another antidepressant with a different pattern of adverse reactions may be considered.

3.10 Health care providers should take into consideration that the risk of self-harm may increase as depression lifts and energy returns with treatment. Health care providers may consider to offer psychological support by scheduling follow-up visits at regular time intervals.

3.11 Substance abuse is relatively common among depressed patients and should not be considered a contraindication to therapy: treating depression can decrease the use of tobacco, alcohol and possibly other medicines of abuse.

3.12 Depressive episodes in patients with bipolar disorder (bipolar depression) generally respond to the same treatment of unipolar depression. However, antidepressant medicines

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may induce a switch from depression to mania. In patients with bipolar depression health care providers should prescribe antidepressants in association with an anti manic medicine, as this combination treatment decreases the risk of switching.

4. Long-term treatment with antidepressants

4.1 According to local circumstances, health care providers may plan regular visits during the first 12 weeks of antidepressant treatment (at least 3 visits are generally recommended), considering that antidepressants may take up to two months to be effective.

4.2 After the acute episode has resolved, it is generally suggested to continue treatment for at least 6-8 months to prevent relapse. Patients at high risk of relapse (e.g. those with 2 or more previous episodes, or those with major depression lasting more than 2 years) should be offered to continue pharmacotherapy for at least 2 years.

> *Antidepressants should be continuously and regularly taken for 6-8 months after recovery*

4.3 Health care providers should prescribed the same dose as used for acute treatment.

4.4 Follow-up visits should be scheduled every 3 to 6 months.

4.5 If depressive symptoms return, health care providers may consider the possibility of adjusting the dosage and check with patient treatment adherence. If symptoms get worse, health care providers should consider a change of medication.

5. Administration of antidepressants

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

5.2 It is generally suggested to start with low doses, and to increase gradually, approaching the target dose over a period of 7 to 14 days.

5.3 Switching from one antidepressant to another should be performed with caution. Health care providers should gradually reduce the dose of the first antidepressant and gradually increase the dose of the new antidepressant.

5.4 Treatment discontinuation should be gradual, with tapering over a period of 2 to 3 months. Abrupt antidepressant withdrawal can cause rebound symptoms.

6. Adverse reactions of antidepressants

6.1 Side-effects associated with tricyclics include sedation, anticholinergic effects (dry mouth, blurred vision, constipation, urinary retention, agitation, confusion), cardiovascular effects (orthostatic hypotension, tachycardia, arrhythmias), prostatism, narrow angle glaucoma and weight gain.

6.2 Side-effects associated with selective serotonin-reuptake inhibitors include activation, agitation, tremor, dizziness, insomnia, nausea, diarrhoea, sexual problems, headache, hyponatraemia, weight loss and rash.

6.3 In patients taking venlafaxine, blood pressure should be regularly checked. Common side-effects associated with venlafaxine include nausea, headache, insomnia, somnolence, dry mouth, dizziness, sexual dysfunction, elevation of blood pressure at high doses. Health care providers should additionally monitor for the signs and symptoms of cardiac dysfunction, particularly in those with known cardiovascular disease.

6.4 Health care providers should take into consideration that antidepressants may induce/ worsen suicide ideas and attempts during early phases of treatment. During these early phases health care providers should plan follow-up visits at short intervals and should consider the possible supporting role of family members and/or hospital admission.

6.5 Hyponatraemia is a rare but potentially serious adverse effect of antidepressants. Health care providers may suspect hyponatraemia if patients develop lethargy, confusion, nausea, muscle cramps and seizures. If hyponatraemia occurs, withdraw antidepressant immediately.

6.6 Tricyclics are associated with higher rates of adverse effects than selective serotonin-reuptake inhibitors, but the difference is small and of uncertain clinical significance.

6.7 Side-effects tend to diminish over time, with the exception of weight gain and sexual dysfunction that may persist longer than other side effects.

6.8 Health care providers should stop treatment gradually, as antidepressants can cause rebound symptoms. Withdrawal symptoms include agitation, anxiety, insomnia, tremor, dizziness, paraesthesia, mood swing and rhinitis. These symptoms are more likely to occur with medicines with a short half life, such as paroxetine.

7. Overdosage of antidepressants

7.1 If antidepressant overdosage is suspected, referral to acute medical facility is recommended.

7.2 The clinical features of tricyclic overdose is characterized by sedation, hypotension, tachycardia, electrocardiogram abnormalities, dry mouth, blurred vision, dilated pupils, urinary retention, absent bowel sounds, convulsions, seizures. The overall incidence of serious cardiovascular arrhythmias is low, while hypotension is more common.

7.3 In general, overdoses with selective serotonin-reuptake inhibitors alone very rarely result in fatality. The clinical features of serotonin-reuptake inhibitors overdose is characterized by vomiting, tremor, drowsiness, tachycardia, electrocardiogram changes, convulsions. At high doses decreased consciousness may occur.

7.4 Antidepressant overdose in combination with alcohol or other medicines appear to be associated with increased toxicity.

7.5 Ingestion of large amounts of venlafaxine may lead to fatalities. Venlafaxine overdose is characterized by sedation, tachycardia, electrocardiogram changes, convulsions.

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8. Special patient populations

8.1 In the elderly low mood may be masked, and anxiety, memory impairment with poor concentration and psychomotor retardation, may be the main symptoms. Since cognitive impairment may result from either depression or dementia, dementia should be considered in the differential diagnosis of depression in older adults. Health care providers may prescribe antidepressant therapy in patients with apparent dementia who meet diagnostic criteria for major depression.

8.2 Since tricyclics are associated with postural hypotension, cardiac conduction abnormalities and arrhythmias, health care providers should ask the patient and/or family member about the existence of cardiovascular abnormalities, and whether drug therapies for cardiac problems have ever been prescribed and taken. If arrhythmia or ischemic heart disease or other serious cardiac problems are present, health care providers should obtain an electrocardiogram before therapy is initiated. If electrocardiogram is not feasible, health care providers may chose not to prescribe tricyclics. Health care providers should consider that the arrhythmogenic potential of tricyclics is dose-related.

8.3 In elderly patients selective serotonin-reuptake inhibitors may increase the risk of gastrointestinal bleeding. Health care providers should cautiously prescribe these agents in elderly patients that concurrently use drugs that may cause bleeding abnormalities (non steroidal anti-inflammatory drugs for example).

8.4 In the elderly, health care providers should prescribe reduced initial doses of tricyclics, with lower final doses. The effective doses of fluoxetine and other selective serotonin-reuptake inhibitors in the elderly may be similar to those for younger adults.

8.5 Antidepressants are hepatically metabolised, so they should be prescribed at lower starting dose, with longer intervals between dosage increases, in patients with liver disease.

8.6 Health care providers should avoid antidepressants in pregnant women. However, if maternal depression is a major concern, an antidepressant may be prescribed. Current evidence suggests that there is no increased risk of malformations in women exposed to fluoxetine and no evidence of teratogenicity. Similarly, there is no convincing evidence that tricyclics are teratogenic in the first trimester, but there is an almost complete absence of formal studies. Rebound symptoms have been observed in some newborns.

8.7 Although less than 10% of the adult therapeutic dose of antidepressants is excreted in breast milk, these agents should be used with care in breast feeding women.

8.8 In children and adolescents there is little evidence that tricyclics are efficacious and, considering the side-effects and risks of toxicity in overdose, they are generally not recommended. Similarly, the balance between benefit and harm is considered unfavourable for the selective serotonin-reuptake inhibitors citalopram, escitalopram, paroxetine, sertraline, and for mirtazapine and venlafaxine. By contrast, fluoxetine has been shown to be effective for treating depressive illness in children and adolescents. However, considering that antidepressants in children and adolescents may induce/worsen suicide ideas and attempts, health care providers should decide use of these medicines on a case-by-case basis. Health care providers should consider that any possible increased risk needs to be balanced against the well established risk of suicide in untreated depression.

9. Potentially relevant interactions

Alcohol and tricyclics. Enhanced sedation may be expected.
Antipsychotics and fluoxetine. Levels of antipsychotics are generally raised.
Barbiturates and tricyclics. Serum levels of amitriptyline are generally reduced.
Carbamazepine and tricyclics. The metabolism of amitriptyline may be accelerated.
Phenytoin and fluoxetine. Levels of phenytoin are generally raised.
Vasoconstrictor sympathomimetics and tricyclics. Response is enhanced, e.g. hypertension and arrhythmias.
Warfarin and fluoxetine. INR (international normalised ratio) may be raised.

10. Essential medicines for depressive disorders

Amitriptyline

Starting dose: 50-75 mg/day orally in divided doses (or as a single dose at night).

Therapeutic dose: 150-200 mg/day orally.

Common adverse effects: dry mouth, constipation, urinary retention, blurred vision and disturbances in accommodation, increased intra-ocular pressure, hyperthermia, drowsiness and increased appetite with weight gain, orthostatic hypotension, tachycardia, sexual dysfunction.

Serious adverse effects: electrocardiogram changes, confusion or delirium, hyponatraemia associated with inappropriate secretion of antidiuretic hormone, peripheral neuropathy, tremor, ataxia, dysarthria, convulsions.

WHO Model List: tablet 25 mg.

Fluoxetine

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Starting dose: 10 mg/day orally. After a week the dose should be increased to 20 mg/day.

Therapeutic dose: 20-40 mg/day orally. Further increases to 60 mg daily may be considered if no improvement is seen after several weeks.

Common adverse effects: gastrointestinal disturbances such as nausea, vomiting, dyspepsia, constipation, diarrhoea, anorexia, weight loss, anxiety, restlessness, nervousness, insomnia; headache, tremor, dizziness, agitation, sexual dysfunction

Serious adverse effects: convulsions, hallucinations, extrapyramidal effects, depersonalisation, panic attacks, hyponatraemia associated with inappropriate secretion of antidiuretic hormone, bleeding disorders, electrocardiogram changes.

WHO Model List: capsule or tablet 20 mg.

Medicines used in bipolar disorders

1.	Definition of bipolar disorders
2.	Preliminary assessment and initial management strategies
3.	Short-term treatment with antimanic medicines
4.	Long-term treatment with antimanic medicines
5.	Administration of antimanic medicines
6.	Adverse reactions of antimanic medicines
7.	Overdosage of antimanic medicines
8.	Special patient populations
9.	Potentially relevant interactions
10.	Essential medicines for bipolar disorders

1. Definition of bipolar disorders

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

1.2 A manic episode is a clinical condition 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, over-familiarity, increased sexual energy, and a decreased need for sleep are often present. 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, or 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 before the disorder becomes full-blown.

1.3 Manic episodes may be associated with significant personal distress and social dysfunction.

1.4 Manic symptoms may be the consequence of a general medical condition or substance abuse.

1.5 Age at first onset ranges between 19 and 29 years. Epidemiological data suggest that it may affect up to 1% of the adult population, with men and women at similar risk. There seems not to be significant differences in prevalence among racial or ethnic groups.

1.6 Almost 40% of people with bipolar disorder have a recurrent manic or depressive episode within 2 years after recovering from the first episode. In people with bipolar disorder the lifetime prevalence of suicide is about 2%.

1.7 Alcohol and medicine abuse frequently complicate the treatment and the clinical course of the disease: the extent of substance abuse varies greatly according to culture, country of residence, and socioeconomic status.

2. Preliminary assessment and initial management strategies

2.1 Health care providers should initially exclude the possibility that an organic illness or a substance abuse disorder is the underlying cause of manic symptoms. A detailed medical and psychiatric history, physical and neurologic examination, and mental status assessment should be carried out.

2.2 If manic symptoms are caused by medical conditions the underlying condition should be managed, with adjunctive psychiatric management for the behavioural problems. If manic symptoms are caused by substance abuse detoxification may be required.

2.3 If feasible, manic patients should be evaluated without delay, considering that agitation and uncooperativeness may be present. Health care providers should be ready to manage the patient's agitation.

2.4 Health care providers may obtain relevant clinical details from individuals who know the patient well. Precipitants of mood change which might be predicted or controlled (life events) should be taken into consideration.

2.5 If physician suspects a manic episode, it is critical to evaluate whether the patient is contemplating self injury.

2.6 Patients with acute manic symptoms contemplating self injury should be intensively

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monitored; monitoring may include admission to an inpatient facility, close supervision by family members or by other individuals who know the patient well.

3. Short-term treatment with antimanic medicines

3.1 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, as these medicines are rapidly effective in mania and are therefore considered antimanic agents. The antimanic medicine valproate has in addition been shown to be rapidly effective in the acute treatment of mania. In less severe manic episodes, lithium may be considered, as this agent has slower onset of action than antipsychotics or valproate.

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

3.3 Before starting antipsychotic therapy, it is generally recommended to check 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, renal function tests, liver function tests, 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 therapies for these medical conditions have been prescribed and taken.

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3.4 Before starting lithium therapy, suggested monitoring includes: renal function tests, thyroid function tests, electrocardiogram, full blood count, pregnancy test. If these laboratory examinations are not feasible, and if health care providers consider that monitoring lithium blood levels is not feasible, lithium should not be prescribed. Health care providers may chose to prescribe an antipsychotic.

3.5 Before starting valproate therapy, suggested monitoring includes: renal and hepatic function tests, 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 therapies for these medical conditions have been prescribed and taken.

> *Lithium, valproate and antipsychotics are beneficial in treating acute mania*

3.6 If benzodiazepines are used for symptomatic effect, they should be gradually discontinued as soon as symptoms improve.

3.7 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 to augment treatment in combination strategies: antipsychotic plus lithium or antipsychotic plus valproate. If adverse reactions are a major problem, health care providers may discuss with the patient and/or family member the possibility to decrease the dose. If adverse reactions persist despite a dose reduction, a switch to another antimanic agent may be considered.

3.8 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 intramuscular) or haloperidol injection (e.g. 5 mg intramuscular). After intramuscular antipsychotic administration, health care providers should monitor blood pressure, pulse, body temperature and respiratory rate.

3.9 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 to antipsychotic therapy. If health care providers prescribe an antidepressant, an antimanic agent should concurrently be prescribed.

3.10 Health care providers should offer information to patients and family members, empathetic listening, reassurance and psychological support. This may help develop a good relationship and a therapeutic alliance that may positively influence the patient subjective well-being and the long-term outcome of the disorder.

4. Long-term treatment with antimanic medicines

4.1 Lithium is considered the medicine of choice in the long-term maintenance phase of bipolar disorder. 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 consider that lithium has a narrow therapeutic index, and blood levels must be monitored. Severe toxic effects can occur when renal excretion is impaired. During lithium treatment, check thyroid function every six months. If monitoring lithium blood levels is not feasible, lithium should not be prescribed.

4.2 In situations where lithium supply may be frequently interrupted, lithium should not be prescribed.

4.3 If lithium is ineffective or poorly tolerated, or if lithium therapy is not feasible, consider valproate. During valproate treatment suggested monitoring includes hepatic function, full blood count and pregnancy test. If these laboratory tests are not feasible, health care providers should remember to regularly take a medical examination, including a recent medical history that may help recognize symptoms suggesting the development of blood or hepatic abnormalities.

4.4 If lithium and valproate are ineffective or poorly tolerated, or if therapy with one of these agents is not feasible, consider carbamazepine. Before and during carbamazepine therapy, suggested monitoring includes: full blood count, liver and renal function tests, pregnancy test. If these laboratory tests are not feasible, health care providers should remember to regularly take a medical examination, including a recent medical history that may help recognize symptoms suggesting the development of blood or renal or hepatic abnormalities.

4.5 Long-term treatment should generally continue for at least two 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 five years.

4.6 Treatment should normally be tapered over at least 2 weeks and preferably longer. Abrupt lithium discontinuation is associated with early manic relapse.

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

5. Administration of antimanic medicines

5.1 Lithium. Health care providers should start with a low-dose (300 mg/day at bedtime), and then increase gradually and monitor blood concentrations every 7 days until level is between 0.6-1.0 milliequivalents (mEq)/litre. Thereafter, blood levels may be checked every 2-3 months (all samples must be taken 12 hours post dose). Renal and thyroid function should be checked every 12 months.

5.2 If treatment adherence is a major problem, lithium treatment may not be feasible.

5.3 Valproate. Start on low-dose (500 mg/day), then increase gradually according to tolerability.

5.4 Carbamazepine. Start with a low-dose (200 mg/day at bedtime), slowly increase until dose 600-1000 mg/day is achieved. Health care providers should consider that the dose may need to be adjusted after two weeks due to hepatic enzyme induction.

6. Adverse reactions of antimanic medicines

6.1 Lithium causes a wide range of adverse reactions including tremor, muscular weakness, polyuria, polydypsia, diabetes insipidus, cardiac arrhythmias, weight gain, cognitive problems, sedation or lethargy, impaired coordination, gastrointestinal distress, hair loss, benign leukocytosis, hypothyroidism, acne and oedema.

> *Lowering the lithium dose may reduce adverse reactions*

6.2 Carbamazepine causes a wide range of adverse reactions including drowsiness, ataxia, diplopia, nausea. Less frequent side-effects include rash, mild leucopenia, mild liver enzyme elevations, mild thrombocytopenia, hyponatraemia and hypoosmolality. Rare, idiosyncratic, serious and potentially fatal side-effects include agranulocytosis, aplastic anaemia, thrombocytopenia, hepatic failure, Stevens–Johnson syndrome, toxic epidermolysis and pancreatitis.

6.3 Diplopia, ataxia and sedation may suggest carbamazepine intoxication.

6.4 Valproate causes a wide range of adverse reactions including gastrointestinal pain, benign hepatic transaminase elevations, tremor and sedation. Patients with hepatic disease may be at increased risk for hepatotoxicity. Mild, asymptomatic leucopenia and thrombocytopenia less frequently occur and are reversible after medicine discontinuation. Rare, idiosyncratic, potentially fatal adverse events include irreversible hepatic failure, haemorrhagic pancreatitis and agranulocytosis.

7. Overdosage of antimanic medicines

7.1 If intoxication is suspected, referral to acute medical facility is recommended.

7.2 The severity of chronic lithium intoxication correlates directly with the serum lithium concentration and may be categorised as mild (1.5 to 2.0 mEq/litre), moderate (2.0 to 2.5 mEq/litre) or severe (>2.5 mEq/litre). Symptoms associated with mild poisoning include lethargy, drowsiness, coarse tremor, muscle weakness, nausea, vomiting, and diarrhoea. Moderate toxicity is associated with confusion, dysarthria, nystagmus, ataxia, myoclonic twitches, and electrocardiogram changes. Severe toxicity, which can be life-threatening, is associated with grossly impaired consciousness, increased deep tendon reflexes, seizures, syncope, renal insufficiency, coma and death.

7.3 The symptoms of carbamazepine overdose include somnolence, tachycardia, atrioventricular conduction defects, seizures, coma, nystagmus, hyporeflexia or hyperreflexia, rigidity, orofacial dyskinesia, and mild respiratory depression.

7.4 The symptoms of valproic acid overdose include hypotension, somnolence, convulsions, coma, respiratory depression, blood dyscrasia.

8. Special patient populations

8.1 In the elderly health care providers should prescribe lower doses.

8.2 If possible, health care providers should not prescribe lithium during pregnancy. Lithium in the first trimester of pregnancy increases the incidence of birth defects, specifically Ebstein's anomaly. Administration during the final months of pregnancy can result in babies who are lithium-toxic at birth.

8.3 Although the teratogenicity of carbamazepine and valproic acid is not entirely clear, their use in pregnancy should be avoided. Both agents are associated with an increased risk of foetal abnormalities, specifically spina bifida. Valproic acid may be more dangerous than carbamazepine.

8.4 If absolutely indicated, the use of low doses of haloperidol may be consider after discussion with the patient and/or family member. Haloperidol is excreted into breast milk.

8.5 Lithium, carbamazepine and valproic acid are excreted in breast milk.

8.6 Lithium is contraindicated in severe renal impairment, as the risk of toxicity is enhanced. Carbamazepine and valproic acid do not generally require dose adjustment in renal impairment.

8.7 Carbamazepine and valproic acid are contraindicated in acute liver disease. In chronic liver disease, health care providers should prescribed lower doses. Lithium does not generally require dose adjustment in liver impairment.

9. Potentially relevant interactions

Angiotensin-converting enzyme inhibitors and lithium. Lithium toxicity may be increased.
Thiazide diuretics and lithium. Renal clearance of lithium is reduced, and levels increased within a few days.
Non-steroidal anti-inflammatory medicines and lithium. Lithium levels should be frequently monitored.
Methyldopa and lithium. Lithium levels may be icnreased.
Increased carbamazepine levels and toxicity produced by: danazol, diltiazem, erythromycin, influenza vaccine, isoniazid, nafimidone, verapamil, viloxazine.

Decreased carbamazepine levels produced by: phenobarbital, phenytoin, primidone, theophylline, tricyclic antidepressants.

Carbamazepine decreases levels or effects of: clonazepam, cyclosporine, dexamethasone, dicoumarol, doxycycline, ethosuximide, haloperidol, pregnancy tests, theophylline, valproic acid, warfarin.

10. Essential medicines for bipolar disorders

Carbamazepine
Starting dose: 200 mg/day orally.
Therapeutic dose: 400-600 mg/day orally.
Common adverse effects: dizziness, drowsiness, ataxia, visual disturbances, confusion, agitation, nausea, vomiting, constipation, leukopenia and other blood disorders, erythematous rash, cholestatic jaundice, hepatitis.
Serious adverse effects: Stevens-Johnson syndrome, toxic epidermal necrolysis, hyponatraemia, agranulocytosis, cardiac conduction disturbances, renal failure.
WHO Model List: tablet 100 mg; tablet 200 mg.

Lithium carbonate
Starting dose: 300 mg/day orally, increasing every 5-7 days according to plasma levels.
Therapeutic dose: 600-1200 mg/day orally, according to plasma levels.
Common adverse effects: gastrointestinal disturbances, fine hand tremor, thirst, polyuria, acne, psoriasis, hypothyroidism, leucocytosis, weight gain, hyperparathyroidism and hypercalcaemia.
Serious adverse effects: nausea, diarrhoea, muscle weakness, drowsiness, ataxia, coarse tremor, muscle twitching, disorientation, renal failure, cardiovascular failure, convulsions, coma.
WHO Model List: capsule or tablet 300 mg.

Valproic acid
Starting dose: 500 mg/day orally in divided doses.
Therapeutic dose: 1000-2000 mg/day orally.
Common adverse effects: nausea, gastric irritation, diarrhoea, weight gain, hyperammonaemia, leucopenia, thrombocytopenia, hair loss, drowsiness, confusion, jaundice, oedema.
Serious adverse effects: ataxia, tremor, vasculitis, hepatic abnormalities, lethargy, anaemia, pancytopenia, pancreatitis.
WHO Model List: tablet 200 mg; tablet 500 mg.

Medicines used in generalized anxiety and sleep disorders

1. Definition of generalized anxiety and sleep disorders

1.1 Anxiety is a condition characterized by the subjective and physiologic manifestations of fear. In anxiety disorders, individuals experience apprehension, but, in contrast to fear, the source of the danger is unknown. The physiologic manifestations of fear include sweating, shakiness, dizziness, palpitations, mydriasis, tachycardia, tremor, gastrointestinal disturbances, diarrhoea, and urinary urgency and frequency.

1.2 If anxiety is generalized and persistent over months but not restricted to any particular environmental circumstances, the term generalized anxiety disorder is usually used. The dominant symptoms are variable but include complaints of persistent nervousness, trembling, muscular tensions, 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.

1.3 The onset of generalized anxiety is usually before the age of 25 years, and the incidence in men is half that in women. The course is fluctuating, and often quite debilitating. In western countries the 12-month prevalence rate is around 3%. Anxiety symptoms may be associated with psychiatric or medical disorders.

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1.4 Major depression occurs in almost two third of patients with generalized anxiety disorder, panic disorder in a quarter and alcohol abuse in more than one third of patients with generalized anxiety disorder.

1.5 Insomnia is a disturbance of normal sleep patterns, with adverse daytime consequences. It affects up to 50% of all adults at some point in their life. The prevalence of insomnia seems to be higher in women and in late life. Individuals with insomnia report difficulty to fall asleep or to remain asleep, and usually feel nonrestored from sleep.

1.6 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.

2. Preliminary assessment and initial management strategies

2.1 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 substances withdrawal (alcohol, opiates, benzodiazepines) can cause anxiety and insomnia. If medical disorders, medicine use or withdrawal is a plausible reason for anxiety, the underlying cause should be removed or treated.

2.2 If medical disorders, medicine use or withdrawal is not a plausible reason for anxiety or insomnia, health care providers might investigate whether major depression or other psychiatric disorders are present. If another psychiatric disorder is present, health care providers should treat that disorder first.

2.3 In individuals with sleep disorders, if no psychiatric comorbidities are present, health care providers may suggest educational 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.

2.4 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.

3. Short-term treatment with benzodiazepines

3.1 Health care providers should initially consider non-pharmacological treatment strategies. Empathic listening, reassurance and guidance should always be offered. Addition-

6

ally, specific psychotherapeutic techniques, such as cognitive-behavioural therapy, are effective measures to reduce anxiety and insomnia, and non specific supportive therapy may initially be offered to patients with uncomplicated generalized anxiety or sleep disorders. Relaxation techniques may additionally be offered.

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

3.3 The use of benzodiazepines is under international control. These agents are internationally regulated by the Convention on Psychotropic Substances, 1971 (United Nations).

3.4 Health care providers should consider that, in addition to international control, benzodiazepine use may be under national control. Health care providers must therefore comply with national, regional and local regulations.

3.5 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 minimise daytime sedation, but they can cause rebound symptomatology more often than agents with longer elimination half-life.

3.6 Ultra-short benzodiazepines are generally not recommended due to the possibility of rebound symptomatology.

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

3.8 According to the WHO EML, 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. Thus diazepam represents benzodiazepines.

3.9 In individuals with insomnia, if short-acting agents such as lorazepam are available, these are generally used when residual sedation is undesirable, if falling asleep is

6

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

a problem, or, when necessary, in elderly patients. Longer-acting benzodiazepines such as diazepam are indicated when early waking is a problem and possibly when an anxiolytic effect is needed during the day or when some impairment of psychomotor function is acceptable.

3.10 Health care providers should consider that in recent years non-benzodiazepine hypnotics such as zopiclone and zolpidem have progressively become widely used in individuals with insomnia. However, these agents may be as likely as the benzodiazepines to cause rebound symptoms, dependence and other adverse reactions.

3.11 In individuals with generalized anxiety disorder health care providers may consider using a benzodiazepine only for a limited course of time. The main objective may be

In patients with generalized anxiety, health care providers may prescribe a benzodiazepine to rapidly relieve symptoms, and consider antidepressants when depression is present or when a long-term therapy is needed

to reduce symptoms enough to allow the patient to engage in treatments based on cognitive-behavioural techniques. A short course (maximum 4 weeks) started at the lowest possible dose for a pre-defined duration of treatment may be used for initial management. Diazepam may be indicated when an anxiolytic effect is needed during the day and an hypnotic effect is required at night.

3.12 Considering that major depression often complicates anxiety symptoms, health care providers should consider using antidepressants. Some tricyclic antidepressants (imipramine, clomipramine) and selective serotonin reuptake inhibitors 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 then treatment may be up-titrated into the normal antidepressant dosage. Treatment response should be assessed after six weeks.

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4. Long-term treatment with benzodiazepines

4.1 Benzodiazepines should not be continued beyond 4 weeks, as chronic use may induce dependence and withdrawal symptoms. Length of therapy should be discussed with patients, and a follow-up visit should be defined in advance (by office visit if possible, or by telephone or by other means) to re-evaluate anxiety and the sleep patterns.

4.2 Health care providers should taper benzodiazepines 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.

5. Administration of benzodiazepines

5.1 Benzodiazepines should be given at the lowest effective dose for as short a period as possible. Diazepam may be given in oral doses of 2 mg one to three times daily, up to oral doses of 5-10 mg twice a day. Lower doses are generally advised in children and adolescents.

5.2 Patients should be advised not to drive or operate machinery while taking benzodiazepines.

5.3 Health care providers should not prescribe two or more benzodiazepines concurrently.

5.4 Health care providers should avoid benzodiazepines in addiction-prone individuals.

5.5 Health care providers should not prescribe benzodiazepines in patients with respiratory failure.

6. Adverse reactions of benzodiazepines

6.1 Drowsiness, sedation and muscle weakness are the most frequent adverse effects of benzodiazepine use. Less frequent effects include vertigo, headache, confusion, depression, dysarthria, changes in libido, tremor, visual disturbances, urinary retention or incontinence, gastrointestinal disturbances, changes in salivation, and amnesia. If patients develop drowsiness, sedation and muscle weakness health care providers may decrease the dosage by one third; patients do not necessarily need to come back to your office to make this dose decrease.

6.2 Health care providers should consider that risk factors for dependence include high dosage, continuous use, use of short half-life benzodiazepines, use in addiction-prone individuals or in those with a history of medicine or alcohol dependence.

6.3 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 and abnormal taste, nausea, vomiting, abdominal cramps, palpitations, mild systolic hypertension, tachycardia, and orthostatic hypotension.

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6.4 Benzodiazepine withdrawal symptoms usually begin within a few hours after withdrawal of a short-acting benzodiazepine, but may not develop for up to 3 weeks after stopping a longer-acting benzodiazepine. Resolution of symptoms may take several days or months. The dependence induced by short- and long-acting benzodiazepines appears to be qualitatively similar although withdrawal symptoms may be more severe with short-acting benzodiazepines. Rebound effects are also more likely with short-acting benzodiazepines.

> *Benzodiazepine withdrawal syndrome may require medical symptomatic support*

7. Overdosage of benzodiazepines

7.1 The outcome of benzodiazepine overdoses is generally favourable unless other medicines, such as alcohol, antipsychotics and antidepressants, have been ingested.

7.2 Benzodiazepine poisoning is associated with rapid impairment of consciousness. A sleep-like state from which the patient can be temporarily roused by appropriate stimuli is generally induced. There is usually little or no respiratory depression, and cardiac rate and rhythm remain normal in the absence of anoxia or severe hypotension.

7.3 If benzodiazepine overdosage is suspected, referral to acute medical facility is recommended.

8. Special patient populations

8.1 Health care providers should use benzodiazepines with care in elderly or debilitated patients who may be more prone to adverse effects. Individuals with impaired liver or kidney function may require reduced doses. Benzodiazepine use should be avoided in severe hepatic impairment. Long-term use may exacerbate underlying dementia in elderly patients.

> *In the elderly and in those with liver and kidney problems health care providers should start slow and go slow*

8.2 Benzodiazepines should be avoided during pregnancy. Health care providers should advise child-bearing women 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 in the infant. Use in the third trimester may be associated with neonatal withdrawal symptoms (floppy infant syndrome). Benzodiazepines should not be given to lactating mothers.

9. Potentially relevant interactions

Alcohol and benzodiazepines. Sedation is enhanced by 20-30%.
Clozapine and benzodiazepines. Sedation and hypotension are enhanced.
Levodopa and benzodiazepines. The effect of levodopa is reduced.

10. Essential medicines for generalized anxiety and sleep disorders

Diazepam
    Starting dose: 2-10 mg/day orally.
    Therapeutic dose: 10-20 mg/day orally.
    For prompt control of severe symptoms: 2-10 mg intramuscular or intravenous injection, may be repeated after 3-4 hours if needed.
    Common adverse effects: drowsiness, sedation, muscle weakness. Diazepam can adversely affect parameters of driving performance in healthy subjects.
    Serious adverse effects: vertigo, headache, confusion, depression, dysarthria, changes in libido, tremor, visual disturbances, urinary retention or incontinence, gastrointestinal disturbances, changes in salivation, and amnesia. Some patients may experience a paradoxical excitation which may lead to hostility, aggression, and disinhibition. Jaundice, blood disorders, and hypersensitivity reactions have been reported rarely. Respiratory depression and hypotension occasionally occur with high dosage and parenteral administration.
    WHO Model List: tablet 2 mg; tablet 5 mg.

6

Medicines used in obsessive-compulsive disorders and panic attacks

1.	Definition of obsessive-compulsive disorder and panic attacks
2.	Preliminary assessment and initial management strategies
3.	Short-term treatment with antidepressants
4.	Long-term treatment with antidepressants
5.	Administration of antidepressants
6.	Adverse reactions of antidepressants
7.	Overdosage of antidepressants
8.	Special patient populations
9.	Potentially relevant interactions
10.	Essential medicines for obsessive-compulsive and panic disorders

1. Definition of obsessive-compulsive disorders and panic attacks

1.1 The essential feature of obsessive-compulsive disorder is recurrent obsessional thoughts or compulsive acts. Obsessional thoughts are ideas, images, or impulses that enter the patient's mind again and again in a stereotyped form. They are almost invariably distressing and the patient often tries, unsuccessfully, to resist them. They are, however, recognized as his or her own thoughts, even though they are involuntary and often repugnant. Compulsive acts or rituals are stereotyped behaviours that are repeated again and again. They are not inherently enjoyable, nor do they result in the completion of inherently useful tasks. Their function is to prevent some objectively unlikely event, often involving harm to or caused by the patient, which he or she fears might otherwise occur. Usually, this behaviour is recognized by the patient as pointless or ineffectual and repeated attempts are made to resist. Anxiety is almost invariably present. If compulsive acts are resisted the anxiety gets worse.

1.2 Frequent symptoms in obsessive-compulsive disorders are contamination concerns with consequent washing rituals, or concerns about self or others with consequent checking rituals. Most patients admit that these thoughts and behaviours are irrational.

7

1.3   The essential feature of panic disorder is recurrent attacks of severe anxiety (panic), which are not restricted to any particular situation or set of circumstances and are therefore unpredictable. As with other anxiety disorders, the dominant symptoms include sudden onset of palpitations, chest pain, choking sensations, dizziness, and feelings of unreality. There is often also a secondary fear of dying, losing control, or going mad. Panic disorder should not be given as the main diagnosis if the patient has a depressive disorder at the time the attacks start; in these circumstances the panic attacks are probably secondary to depression. Between attacks patients show persistent concern about having another panic attack, and are very worried about the possible implications of such attacks.

1.4   Obsessive-compulsive and panic disorders often start between late adolescence and the mid-30s. In western countries lifetime prevalence is around 1–3%. While obsessive-compulsive disorder is similarly distributed between males and females, panic attacks are more common in women. Both disorders are associated with reduced social or occupational functioning in the long-term.

2. Preliminary assessment and initial management strategies

2.1   Health care providers may use specific questions to recognize the presence of obsessions (Do you have unpleasant thoughts that keep coming into your mind, even though you don't want them?) and compulsions (Do you have to do things over and over, even though you don't want to?).

2.2   Initial treatment of obsessive-compulsive and panic disorders may be based on non-pharmacological interventions, including cognitive behavioural therapies. Health care providers may discuss with the patient the feasibility of a psychological intervention, considering patient preferences, severity of illness, co-morbidity, concomitant medical illnesses, substance abuse and history of previous treatments.

Psychological interventions, such as cognitive behavioural treatments, are effective in patients with obsessive-compulsive and panic disorders

7

2.3   If cognitive-behavioural therapy is not feasible, education and non specific supportive therapy may be offered. Health care providers should consider that empathic listening, reassurance and guidance may positively affect the patient subjective well-being. Information should be provided to patients and/or family members about the etiology, risk factors, and natural course of panic disorder.

3. Short-term treatment with antidepressants

3.1   Cognitive-behavioural therapy is first line of treatment. If patients do not respond to cognitive-behavioural interventions, or if cognitive-behavioural interventions are not

feasible, health care providers may consider a serotonin reuptake inhibitor. All serotonin reuptake inhibitors are probably similarly effective.

3.2 According to the WHO EML, essential medicine for obsessive-compulsive and panic disorders is clomipramine.

3.3 Clomipramine may be prescribed at low doses initially, and then treatment may be up-titrated into the normal antidepressant dosage. Treatment response should be assessed after 12 weeks. If no improvement is seen after 12 weeks, health care providers may discuss with the patient the possibility to increase the dose. In individuals who do not improve despite the dose increase, a switch to another antidepressant may be considered.

3.4 Benzodiazepines are second-line agents in the pharmacological treatment of panic disorder. Although benzodiazepines are associated with significant improvement over the first weeks of therapy, tolerance usually limits their long-term usefulness. Panic symptoms may quickly return after benzodiazepines are withdrawn. Benzodiazepines are usually not indicated in people with obsessive-compulsive symptoms. Health care providers should consider that the use of benzodiazepines is under international control and may be under national control.

3.5 In addition to pharmacological treatment and/or specific cognitive-behavioural interventions, health care providers may consider to provide psychological support by scheduling follow-up visits at regular intervals. This may help develop a good health care provider – patient relationship and a therapeutic alliance that may positively influence the long-term outcome of the disorder.

4. Long-term treatment with antidepressants

4.1 Health care providers should discuss with the patient the possibility to prolong antidepressant treatment for one year, at a dose that may be reduced up to 50% of that used during the acute episode. When treatment is discontinued, withdrawal symptoms may occur.

4.2 If benzodiazepines are prescribed, these should not be continued beyond 4 weeks, as chronic use may induce dependence and withdrawal symptoms. Health care providers should taper benzodiazepines very gradually.

5. Administration of antidepressants

5.1 Health care providers should not prescribe two or more antidepressants concurrently.

7

5.2 Clomipramine may be given in divided doses throughout the day, but since it has a prolonged half-life, once-daily dosage regimens are also suitable, usually given at night.

5.3 Switching from one antidepressant to another should be performed with caution. Health care providers should gradually reduce the dose of the first agent while gradually increasing the dose of the new antidepressant.

6. Adverse reactions of antidepressants

6.1 See Medicine used in depressive disorders.

7. Overdosage of antidepressants

7.1 See Medicine used in depressive disorders.

8. Special patient populations

8.1 See Medicine used in depressive disorders.

9. Potentially relevant interactions

9.1 See Medicine used in depressive disorders.

10. Essential medicines for obsessive-compulsive and panic disorders

Clomipramine
Starting dose: 10-25 mg/day orally.
Therapeutic dose: 150-200 mg/day orally.
Common adverse effects: dry mouth, constipation, urinary retention, blurred vision and disturbances in accommodation, increased intra-ocular pressure, hyperthermia, drowsiness and increased appetite with weight gain. Cardiovascular adverse effects may include orthostatic hypotension and tachycardia. Headache, tremor and ataxia have additionally been reported.
Serious adverse effects: confusion or delirium, mania or hypomania, behavioural disturbances, sexual dysfunction, changes in blood sugar concentrations, hyponatraemia associated with inappropriate secretion of antidiuretic hormone.
WHO Model List: capsule 10 mg; capsule 25 mg.

7

Medicines used in alcohol and opioid dependence

1.	Definition of alcohol and opioid dependence
2.	Preliminary assessment and initial management strategies
3.	Short-term treatment (alcohol dependence and withdrawal)
4.	Short-term treatment (opioid dependence and withdrawal)
5.	Long-term treatment
6.	Administration
7.	Adverse reactions
8.	Overdosage
9.	Special patient populations
10.	Potentially relevant interactions
11.	Essential medicines for opioid dependence

1. Definition of alcohol and opioid dependence

1.1 Among the disorders due to psychoactive substance use, the dependence syndrome, the disorders of acute effects (intoxication and overdose), and the withdrawal states are the most common clinical conditions that may require pharmacological treatment. The scope of this section is limited to alcohol and opioid dependence and withdrawal.

1.2 The term "dependence syndrome" refers to a cluster of behavioural, cognitive, and physiological phenomena that develop after repeated substance use and that typically include a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal state.

1.3 The term "withdrawal state" refers to a group of symptoms of variable clustering and severity occurring on absolute or relative withdrawal of a substance after repeated, and usually prolonged and/or high-dose, use of that substance. The withdrawal state in alcohol dependence usually presents with symptoms of sweating, tremor, nausea and vomiting, elevated blood pressure, tachycardia, anxiety and agitation, craving for alcohol, sleeplessness, and may be complicated by convulsions or delirium tremens.

8

The duration of alcohol withdrawal, that usually develops after 24-48 hours after absolute or relative withdrawal from alcohol, lasts 1-3 and sometimes up to 5-7 days. Withdrawal state in opioid dependence is characterized by yawning, watering eyes, sweating, irritability, tremor, diarrhoea, chills, cramps and muscle aches, increased blood pressure and heart rate, and can lasts up to 7-10 days.

1.4 Alcohol dependence is common, affecting approximately 6.5% of men and 1.5% of women. It often develops in early adulthood, but can start at any age after repeated continued exposure to alcohol beverages. It predominantly affects men, representing gender differences in drinking patterns among men and women in different cultures. The prevalence of alcohol dependence varies in different countries according to the prevalence and patterns of alcohol consumption, but in some countries, the 12-month prevalence of alcohol dependence among adult men is as high as 10-15%.

1.5 Opioid dependence develops after a period of regular use of opioids, which is a necessary, but not sufficient, condition for developing opioid dependence. Common substances for opioid dependence are heroin and pharmaceutical opioids. To maximize their effect, opioids are often intravenously injected, but they can also be inhaled or taken orally. Heroin users have a mortality risk 13 times higher than the average in the same age group, even without taking into consideration increased mortality associated with HIV and other blood-borne infectious diseases, like hepatitis B and C. This increase

In some countries heroin injecting accounts for 25-33% of deaths in young adult males

in mortality is mainly due to opioid overdose, followed by violent deaths. The 12-month prevalence of opioid dependence in adult populations usually does not exceed 0.5%.

2. Preliminary assessment and initial management strategies

2.1 In populations where drinking of alcohol beverages is culturally acceptable, all patients should be asked about their alcohol use. The following question can be used: "How often do you have 6 or more drinks on one occasion?". The objective of screening is to identify patients at higher risk of alcohol use disorders for further diagnosis and treatment.

2.2 In health care settings in which drug use is common, or for presenting complaints for which drug use is a common precipitating factor, all patients should be asked about their drug use, or screened for drug use with instruments such as the WHO-ASSIST.

2.3 Diagnosis of individual substance use disorders should be made on the basis of history, examination and investigations. The substance use history should examine the level and pattern of alcohol consumption, real and potential harms from substance use and the context in which substance use occurs. Health care providers may quantify the level

8

of risk of harm from the consumption of alcohol and determine if any substance use disorders are present. The physical examination should check for the substance use effects of acute intoxication or withdrawal, and for effects of chronic substance use, and method of use (i.e. needle marks), and co-occurring conditions. If feasible, health care providers may investigate for substance-induced organ damage, and may include tests to determine the presence of substances in urine or other bodily fluids.

2.4 Health care providers should take the medical history in a non-judgemental and non-confrontational way. The substance use history should examine the level and pattern of substance use, the context in which substance use occurs, harm that has occurred as a result of substance use, the patient's perspective on their substance use (including their motivations for continuing and motivations for changing their pattern of substance use), and their previous attempts to change their pattern of substance use.

2.5 Patients with alcohol or opioid dependence may also be taking other psychoactive substances, like benzodiazepines or cannabis, and often have tobacco dependence as well. It is necessary to explore, in addition to the history of taking opioids or alcohol consumption, other substance use, particularly when pharmacotherapy involving methadone or buprenorphine is planned, in view of their interaction with other substances with a potential to cause a respiratory depression.

2.6 Patients with substance use disorders frequently also have other mental disorders. Health care providers should look for these disorders, exploring the link with the substance use disorders.

2.7 Health care providers should diagnose and treat any comorbid medical and psychiatric conditions. In some situations, substance use may be in response to some painful conditions.

> *Patients with substance use disorders are at increased risk of a range of medical and psychiatric disorders*

2.8 The diagnosis of harmful use of alcohol or opioids require interventions from health care professionals, but pharmacological treatment is justified only for treatment of alcohol or opioid dependence, management of withdrawal states, and some substance induced clinical conditions.

3. Short-term treatment (management of alcohol withdrawal, Wernicke-Korsokoff syndrome and commencement of relapse prevention medication for alcohol dependence)

3.1 Health care providers should consider that people with alcohol dependence usually find it very difficult to return to low levels of alcohol consumption, and that even these low

8

levels of consumption can still contribute to end organ (i.e. brain and liver) damage. Consequently, the target level of alcohol consumption for people with alcohol dependence should be zero alcohol.

3.2 Not all people dependent on alcohol experience alcohol withdrawal symptoms. Many will experience only mild withdrawal symptoms such as anxiety, insomnia, headache and agitation that resolve without need for medication. Some people, on the other hand, will experience severe anxiety, agitation, insomnia, headache, tremors, sweating, tachycardia, hypertension, and hallucinations, seizures and delirium (delirium tremens). People more likely to experience severe withdrawal are those who drink higher amounts, such as

Untreated delirium tremens has been reported to have up to a 30% mortality

greater than 100 grams alcohol per day, have had multiple episodes of alcohol withdrawal in the past, have concomitant benzodiazepine or other sedative drug use, and have concomitant medical illnesses.

3.3 Benzodiazepines are the main treatment for alcohol withdrawal. Used in the 5 days following the cessation of alcohol, in doses proportional to the severity of the withdrawal syndrome, they reduce the discomfort and complications of alcohol withdrawal, including seizures and delirium. Long acting benzodiazepines such as diazepam are preferable to short acting benzodiazepines.

3.4 People with mild or moderate alcohol dependence can be withdrawn from alcohol at home. In this setting, patients should receive 5-20 mg diazepam three to four times daily, depending on the severity of withdrawal, tapering to zero over 4-5 days. Patients needing higher doses of diazepam should be treated in a residential setting. Because of their abuse potential, benzodiazepines should not be continued for more than a week. The initial prescription should not be for more than 40 mg diazepam per day, unless the patient is known to experience severe withdrawal symptoms and can tolerate high doses of benzodiazepines.

3.5 In residential settings, patients can be given 20 mg diazepam every 1-2 hours until the patient is calm and mildly sedated, with reducing doses given as needed over the following 4-7 days. Use of more than 120 mg diazepam in a 24 hours period warrants the involvement of a specialist in the treatment of alcohol use disorders.

8

3.6 Health care providers should correct nutritional and electrolyte deficiencies. This typically involves: 100 mg thiamine intramuscularly daily for five days followed by 100 mg daily orally indefinitely; and oral potassium, magnesiuim and zinc supplementation during withdrawal.

3.7 Patients should be placed in low stimulus environments (i.e quiet and dimly lit) and given adequate rehydration. Patients should not be given dextrose before thiamine.

3.8 Health care providers should consider that Wernicke-Korsakoff encephalopathy is common and does not always present with the classic triad of ataxia, confusion and ophthalmoplegia; any altered mental state, ataxia, ophthalmoplegia, or memory disturbance should be provisionally considered Wernicke-Korsakoff encephalopathy. Health care providers should be treated with diluted infusions of high dose thiamine 3 times daily for 2 days, and continued daily for 5 days if there is any response to treatment.

3.9 There are several medications which have been shown to be effective in reducing relapse to alcohol dependence, noteably: acamprosate, disulfiram and naltrexone. These medicines are not included in the WHO Model list of Essential Medicines.

3.10 Acamprosate inhibits transmission at NMDA - glutamatergic receptors and stimulates, to a lesser extent, $GABA_A$ receptors which are both involved in alcohol dependence and alcohol withdrawal. In this way it is thought to reduce cravings associated with alcohol dependence.

3.11 Disulfiram inhibits the action of the enzyme acetaldehyde dehydrogenase, thus inhibiting the main metabolic pathway of alcohol. If alcohol is consumed, the build up of toxic acetaldehyde leads to an unpleasant reaction including throbbing headache, facial flushing, nausea, vomiting, tachycardia, hypotension, dyspnoea, blurred vision, weakness and confusion. In severe cases it can be fatal, particularly in the elderly, and those with ischaemic heart disease. The knowledge of these severe adverse reaction is enough to prevent alcohol consumption in some people. In others, the first experience of the alcohol-disulfiram reaction will prevent relapse. Patients who relapse usually stop taking their disulfiram and should not be encouraged to recommence until they have ceased alcohol consumption. Treatment with disulfiram should be supervised and regularly reviewed.

3.12 Naltrexone is a high affinity opioid antagonist. It is thought to act by reducing both the craving for alcohol and the enjoyment of alcohol as medicated by opioid receptors. Naltrexone can cause nausea when commenced, although this normally resolves in the first week of treatment.

4. Short-term treatment (management of opioid withdrawal and commencement of agonist maintenance treatment)

4.1 The goals of the treatment of opioid dependence more broadly include preventing the health and social problems associated with non-prescribed opioid use and reducing non-prescribed opioid use.

4.2 The most effective pharmacological treatment of opioid dependence is opioid agonist maintenance therapy with methadone, followed by opioid agonist maintenance therapy with

8

buprenorphine. Before commencing opioid agonist maintenance therapy, patients should be assessed to confirm the diagnosis of opioid dependence. It is important to make a correct diagnosis because opioid agonist maintenance treatment can cause harm in people who are not opioid dependent. The diagnosis should be made firstly on the basis of the history and supported by evidence from physical examination, investigations, or by confirmation of the history from other sources.

Opioid agonist maintenance therapy reduces drug use, criminal activity and reduces the risk of contracting HIV

4.3 Opioid withdrawal symptoms include nausea, stomach cramps, muscular tension, muscular spasm/twitching, aches and pains, and insomnia. Symptoms usually reach their peak 32-72 hours after the last dose. Treatment of opioid withdrawal reduces the severity of the opioid withdrawal syndrome, increasing the chances of completing opioid withdrawal and of commencing subsequent treatment options.

4.4 According to the WHO EML, essential medicine for opioid dependence are methadone and buprenorphine. These agents can be used for both opioid withdrawal and maintenance treatment. Maintenance treatment must be provided in combination with services which can provide psychosocial support.

4.5 Methadone is subject to international control under the Single Convention on Narcotic Drugs (1961). Buprenorphine is subject to international control under the Convention on Psychotropic Substances (1971). The International Narcotics Control Board (INCB) is charged with monitoring the compliance by Governments with the above international treaties, ensuring on the one hand that controlled substances are available for medical and scientific use and on the other hand that diversion from licit sources to illicit traffic does not occur.

4.6 Health care providers should warn patients about the risk of toxicity and overdose associated with methadone use. While opioid withdrawal is not a life-threatening condition, opioid toxicity is.

5. Long-term treatment

5.1 The optimal duration of therapy with acamprosate, disulfiram and naltrexone is uncertain. The continued use should be assessed on an individual basis. In people who are abstinent, there is little data to support their ongoing use beyond one year of abstinence. By contrast, those who do relapse to alcohol dependence, statistically the majority, should not consider that they are unresponsive to the medication, and should still consider either the same or a different relapse prevention medication on future attempts to stop drinking.

5.2 The optimal duration of opioid agonist maintenance treatment is not known, but it can be continued in the long-term. Cessation of opioid agonist maintenance treatment is

8

associated with a high risk of relapse and overdose and the timing of withdrawal from opioid agonist maintenance treatment should be made on a case-by-case basis.

5.3 When withdrawing from opioid agonist maintenance treatment, health care providers should establish with the patient a flexible plan of gradual dose decreases. This plan needs to be regularly reviewed, taking into consideration the patient's readiness for total abstinence.

5.4 Health care providers should consider that psychosocial interventions play an important role in the treatment of alcohol and opioid dependence. Basic social support includes addressing the many specific social needs that patients may have, including housing, food, company, recreation, employment, and legal assistance. Exploring the psychosocial needs and linking with services available in the community to meet those needs is one of the key roles of psychosocial assistance.

6. Administration

6.1 For adults 18-65 years weighing 60 kg and over, the starting dose of acamprosate is 666 mg three times daily; for adults less than 60 kg, the dose should be reduced to 666 mg (morning), 333 mg (midday) and 333 mg (night).

6.2 Health care providers, before starting treatment with disulfiram, must ensure that no alcohol has been consumed for at least 24 hours. Disulfiram should be started at 800 mg as a single dose on first day, reducing over 5 days to 100-200 mg daily. Patients should ideally have supervision during treatment, by a family member or by someone who knows the patient well.

6.3 Naltrexone is usually commenced after detoxification at a standard dose of 50 mg daily, although doses from 25 to 100 mg have been used. Higher doses may result in liver damage.

6.4 Health care providers should consider that the use of methadone and buprenorphine for opioid dependence should be supervised during the first three months or until stability is achieved. Daily dispensing is usually recommended.

6.5 Health care providers should prescribe methadone in the oral liquid formulation. Tablets should not be prescribed because they may be crushed and inappropriately injected.

6.6 Health care providers may initially prescribe methadone in the range of 10-20 mg daily, depending on the level of tolerance. Observing patients 2-3 hours after their dose enables the best assessment of the degree of tolerance to opioids. If patients have significant opioid

8

withdrawal symptoms 2-3 hours after their dose of methadone, then they should be given an additional 5-10 mg methadone and a corresponding increase in their next daily dose. If patients are sedated after their dose of methadone, then the next daily dose should be reduced, and patients should be observed until the patient is no longer sedated. Dose increases should not exceed 5-10 mg daily and 30 mg per week. Treatment stabilisation is usually achieved within 6 weeks but may take longer. In the treatment of opioid withdrawal, the dose on the first day is the same, with subsequent doses reducing over 1-3 weeks.

> *Starting doses of methadone above 20 mg should be prescribed with caution because of the risk of overdose and death*

6.7 If one of two doses of methadone are missed the patient can be maintained on the same dose. If three doses are missed the next methadone dose should be reduced by 25% to adjust for the possible reduction in tolerance. If it is well tolerated, doses can return to previous dose levels. If four doses are missed the next dose should be reduced by 50% to adjust for the potential reduction in tolerance. If the dose is well tolerated doses can be increased over several days to previous levels. If more than four doses are missed, patients should resume induction from baseline.

6.8 Methadone can be administered daily for most patients. In approximately 20% of patients, methadone is metabolized more quickly and does not produce stable opioid effects over the 24 hours between doses. In such cases methadone can be administered twice a day, dividing the dose in two. When it is too difficult to pick up the medication twice a day, or when take home doses are not suitable, then buprenorphine should be considered as an alternative.

6.9 In heroin users, health care providers may initially prescribe 8 mg buprenorphine in patients experiencing some opioid withdrawal symptoms. If no withdrawal symptoms are present, 4 mg buprenorphine may be prescribed. Dose increases should not exceed 2-4 mg at a time, up to a maximum daily dose of 32 mg. Maintenance dose is usually in the range of 12-24 mg daily.

6.10 After a satisfactory period of stabilization has been achieved the frequency of buprenorphine dosing may be decreased to dosing every other day at twice the individually titrated daily dose. For example, a patient stabilized to receive a daily dose of 8 mg may be given 16 mg on alternate days, with no medication on the intervening days. However, the dose given on any one day should not exceed 32 mg. In some patients, after a satisfactory period of stabilization has been achieved, the frequency of dosing may be decreased to three times a week (for example on Monday, Wednesday and Friday). The dose on Monday and Wednesday should be twice the individually titrated daily dose, and the dose on Friday should be three times the individually titrated daily dose, with no medication on the intervening days. However, the dose given on any one day should not exceed 32 mg. In

8

the management of opioid withdrawal using buprenorphine, the dose over the first 3 days should be similar to opioid maintenance treatment, tapering rapidly thereafter. One suggested schedule is Day 1 – 6 mg, day 2-3 – 10+/-2 mg, day 4 – 8+/-2 mg, day 5 – 4 mg.

6.11 Health care providers may need to switch from buprenorphine to methadone. Methadone should be started 24 hours after the last dose of buprenorphine. When commencing methadone from buprenorphine doses of 8 mg daily and above, commence with 30 mg methadone daily. From buprenorphine doses of 4-8 mg daily, commence with 20-30 mg methadone daily. With buprenorphine doses below 4 mg daily, commence with less than 20 mg methadone daily.

7. Adverse reactions

7.1 Adverse reactions associated with acamprosate treatment include diarrhoea, nausea, vomiting, abdominal pain, pruritus, occasionally maculopapular rash, rarely bullous skin reactions, fluctuation in libido.

7.2 Adverse reactions associated with disulfiram treatment include drowsiness, fatigue, nausea, vomiting, halitosis, reduced libido, rarely psychotic reactions, allergic dermatitis, peripheral neuritis, hepatic cell damage.

7.3 Adverse reactions associated with naltrexone treatment include nausea, vomiting, abdominal pain, anxiety, nervousness, sleeping difficulties, headache, reduced energy, joint and muscle pain; less frequently, loss of appetite, diarrhoea, constipation, increased thirst, chest pain, increased sweating and lacrimation, irritability, dizziness, chills, delayed ejaculation, rash; occasionally, liver function abnormalities.

7.4 Methadone use is a risk factor for QT interval prolongation. It is additionally possible that methadone combined with other QT-prolonging agents may increase the likelihood of QT prolongation. Health care providers may consider an ECG at baseline and during treatment in individuals with other risk factors for QT prolongation.

7.5 Buprenorphine may cause changes in liver function in individuals with hepatic impairment. Monitoring of hepatic function should be considered in individuals at risk.

8. Overdosage

8.1 Health care providers should consider that methadone should not be given to patients showing signs of intoxication, especially due to alcohol or other CNS depressant drugs. Risk of fatal overdose is enhanced when methadone is combined with alcohol or other respiratory depressant drugs.

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8.2 Health care providers should consider that buprenorphine should not be given to patients showing signs of intoxication, especially due to alcohol or other CNS depressant drugs. Risk of fatal overdose is enhanced when buprenorphine is combined with alcohol or other respiratory depressant drugs. Overdose of buprenorphine is usually safer than overdose of methadone.

8.3 High doses of naltrexone have resulted in tremors, tachycardia, dizziness, insomnia, fatigue and agitation. High doses of naltrexone have been associated with elevations of liver transaminases.

8.4 In limited cases of overdose, doses of up to 56 grams of acamprosate (normal dose approximately 2 g/day) were generally well tolerated, and the only associated symptom was diarrhoea.

8.5 Lethargy, ataxia, seizures, and coma have occurred after acute ingestion of 2.5 to 3 grams of disulfiram in children. These may be preceded by vomiting, lethargy, tachypnoea, tachycardia, EEG abnormalities, and ketosis.

8.6 High doses of buprenorphine have resulted in transient changes in hepatic transaminases.

9. Special patient populations

9.1 Acamprosate should be used with caution and at lower doses in individuals with renal or hepatic impairment.

9.2 Acamprosate is not recommended in individuals who are pregnant or breastfeeding.

9.3 Disulfiram is contra-indicated in individuals with coronary heart disease, cardiac failure, history of cerebrovascular accidents, hypertension, psychosis, severe personality disorders, suicide risk.

9.4 Naltrexone is contra-indicated in individuals with acute hepatitis or liver failure. Health care providers should cautiously prescribe naltrexone in individuals with hepatic and renal impairment. If feasible, liver function tests should be routinely carried out.

9.5 Disulfiram is contra-indicated in individuals who are pregnant or breastfeeding.

9.6 Naltrexone is not recommended in individuals who are pregnant or breastfeeding.

9.7 Methadone and buprenorphine should not be given to patients showing signs of intoxication or sedation, due to the risk of sedative overdose. The risks of methadone

8

and buprenorphine use in opioid dependent patients who are frequently intoxicated with sedatives such as alcohol and benzodiazepines, needs to be balanced against the benefits of treatment.

9.8 The metabolism and elimination of methadone and buprenorphine may be affected by either hepatic or renal dysfunction in which case the dose or dosing frequency should be reduced accordingly.

9.9 In patients with respiratory insufficiency, methadone and buprenorphine may reduce the respiratory drive.

9.10 Methadone and buprenorphine can be used in individuals who are pregnant or breast-feeding.

10. Potentially relevant interactions

Alcohol and disulfiram. See above.
Warfarin and disulfiram. Decreased prothrombin time.
Medications that prolong the QT interval and methadone. Increased risk of QT prolongation-associated cardiac arrhythmias
Antiretrovirals and methadone. Altered plasma levels of methadone and antiretrovirals. Dose adjustment may be required.
Antiretrovirals and buprenorphine. Altered plasma levels of buprenorphine and antiretrovirals. Dose adjustment may be required.

11. Essential medicines for opioid dependence

Methadone hydrochloride
Starting dose: The initial dose of methadone should not be more than 20 mg a day and should be determined for each patient based on the severity of dependence, the level of tolerance to opioids, use of other psychoactive substances such as benzodiazepines or alcohol, as well as on the other relevant clinical factors.
Therapeutic dose: Once it has been established that the initial dose is well tolerated, the methadone dose should be gradually increased until the patient is comfortable and not using heroin or other illicit opioids. The rate of increase should be individually assessed, and should generally not be faster that 10 mg every few days. On average, methadone maintenance doses range from 60 to 120 mg daily, sometimes higher dosage is required.
Adverse effects: anorexia, nausea, vomiting (particularly in initial stages), constipation; euphoria, hallucinations, dizziness, drowsiness, confusion, headache; dry mouth, spasm of urinary or biliary tract; hypotension, postural

8

hypotension, vertigo, bradycardia, tachycardia, palpitations, headache, sweating, miosis, hypothermia; decreased libido; rash, facial flushing, urticaria, pruritus.
Serious adverse effects: respiratory depression.
WHO Model List: Oral solution, concentrate (Powder for oral concentrate), methadone hydrochloride 5 mg/ml, 10 mg/ml; Oral solution, methadone hydrochloride 5 mg/5 ml, 10 mg/5 ml.

Buprenorphine hydrochloride

Starting dose: 2-8 mg a day, sublingually, and the dose should be determined for each patient based on the severity of dependence, the level of tolerance to opioids, the presence or absence of opioid withdrawal features, the use of other psychoactive substances such as benzodiazepines or alcohol, as well as on the other relevant clinical factors.

Therapeutic dose: For management of opioid withdrawal state, 4-32 mg a day, sublingually, with subsequent reduction of dosage by 1-4 mg over three to fourteen days. Average buprenorphine maintenance dose should be at least 8 mg per day.

Adverse effects: anorexia, nausea, vomiting (particularly in initial stages), constipation; euphoria, hallucinations, dizziness, drowsiness, confusion, headache; dry mouth, spasm of urinary or biliary tract; hypotension, postural hypotension, vertigo, bradycardia, tachycardia, palpitations, headache, sweating, miosis, hypothermia; decreased libido; rash, facial flushing, urticaria, pruritus.
Serious adverse effects: respiratory depression.
WHO Model List: Sublingual Tablets, buprenorphine hydrochloride 2 mg, 8 mg.

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8.2 Before prescribing antipsychotics to elderly patients health care providers should take a detailed medical history and a medical examination, and should additionally ask about concurrent drug therapies.

> *In the elderly one half to one third the adult dose is generally recommended*

8.3 If possible, antipsychotics should be avoided during pregnancy, particularly during the first trimester. If absolutely indicated, the use of low doses of haloperidol may be consider after discussion with the patient and/or family member. Haloperidol is excreted into breast milk.

9. Potentially relevant interactions

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Alcohol and antipsychotics. Enhanced central nervous system depression may be expected, with impaired concentration, drowsiness and lethargy.
Anticonvulsants and antipsychotics. Antipsychotics lower the seizure threshold and may thus antagonise anticonvulsant action.
Barbiturates and antipsychotics. Enhanced sedative effects is expected.
Carbamazepine and antipsychotics. Carbamazepine reduces haloperidol levels.
Levodopa and antipsychotics. The therapeutic effect of levodopa is antagonised by antipsychotics and vice versa.

10. Essential medicines for psychotic disorders

Chlorpromazine
    Starting dose: 25-50 mg/day orally.
    Therapeutic dose: 75-300 mg/day orally, up to 1 g daily in acute psychoses.
    For prompt control of psychotic symptoms: 25 mg intramuscular injection, may be repeated after one hour if needed, subsequent doses should be 25-50 mg orally 3 times a day. Chlorpromazine injections should not be used intravenously.
    Common adverse effects: akathisia, dystonic extrapyramidal effects, parkinsonian extrapyramidal effects, tardive dyskinesia, tardive dystonia, dry mouth, blurred vision, constipation, urinary retention, nasal congestion, dizziness, drowsiness, orthostatic hypotension, photosensitivity. Intramuscular injection may be painful, may cause hypotension and tachycardia.
    Serious adverse effects: blood dyscrasias, agranulocytosis, leukocytopenia, thrombocytopenia, cholestatic jaundice, neuroleptic malignant syndrome, paralytic ileus, priapism, electrocardiogram changes, including QT prolongation and torsades de pointes, seizures.
    WHO EML: tablet 100 mg; oral liquid 25 mg/5 ml; injection 25 mg.

This manual attempts to provide simple, adequate and evidence-based information to health care professionals in primary health care especially in low- and middle-income countries to be able to provide pharmacological treatment to persons with mental disorders. The manual contains basic principles of prescribing followed by chapters on medicines used in psychotic disorders; depressive disorders; bipolar disorders; generalised anxiety and sleep disorders; obsessive-compulsive disorders and panic attacks; and alcohol and opioid dependence.