World Health Organization

Eastern Mediterranean Region

Pharmacological treatment of priority mental, neurological and substance use disorders in non-specialized health care

A job aid for supporting implementation of the mhGAP guidelines

mhGAP

Mental Health Gap Action Programme

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Contents

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Preface

Mental, neurological and substance use (MNS) disorders are common in all regions of the world, affecting every community and age group across all countries, regardless of income. Some 10% of the global burden of disease is attributed to these disorders, but the World Health Organization (WHO) estimates that only 29% of people with psychosis and 40% of people with depression receive mental health services.

The gaps in treatment vary across countries and from one mental health condition to another. For example, while 70% of people with psychosis are reported to be treated in high-income countries, only 12% receive mental health care in low-income countries. For depression, the gaps in service coverage are wide across all countries: even in high-income countries, nearly half of people with moderate to severe depression do not receive formal mental health care.

In 2009, WHO published the first edition of *Pharmacological treatment of mental disorders in primary health care*. This manual was a reference source to assist physicians working in primary health care by increasing their knowledge and improving their routine clinical practice in using medicines for mental disorders.

Since then, WHO has launched the Mental Health Gap Action Programme (mhGAP), which aims to scale up services for MNS disorders, in particular in low- and middle-income countries. The programme asserts that with proper care, including psychosocial and pharmacological interventions, tens of millions of people could be treated for depression, anxiety disorders, psychosis, substance use disorders, dementia and epilepsy, be discouraged from suicide and begin to lead normal lives, even where resources are scarce.

The mhGAP Intervention Guide (mhGAP-IG) is a model guide to help non-specialized health care providers working in first- and second-level health care facilities to manage priority MNS disorders. It also indicates where consultation and supervision by specialists are required in the management of these disorders. Similarly, the mhGAP Humanitarian Intervention Guide (mhGAP-HIG) contains first-line management recommendations for MNS conditions for non-specialist health care providers in humanitarian emergencies, where access to specialists and treatment options is limited. The mhGAP guides present tools for clinical decision-making and management for each priority disorder. The management sections outline psychosocial and pharmacological interventions.

This job aid aims to serve as a detailed reference on pharmacological treatments for priority mental disorders for non-specialized health care providers who are trained on the mhGAP guidelines. Non-specialized health care providers, in this context, include primary care physicians (family physicians, GPs), non-specialist doctors at secondary care level and nurses in countries where they have prescribing rights.

In addition, other WHO guidelines, such as on the identification and management of substance use and substance use disorders in pregnancy, and international guidelines, such as the NICE and Maudsley guidelines, have been consulted where needed. In addition, reference to the WHO Model List of Essential Medicines has been made for priority disorders.

This manual covers pharmacological treatments for all priority disorders including clinical indications, dosage regimens, side-effect profiles, commonly encountered drug interactions, and protocols for safe monitoring and stopping medicines. Details are included of some serious side-effects, such as serotonin syndrome and neuroleptic malignant syndrome. It also covers a wide range of medicines that are prescribed by specialists but which may need to be managed by non-specialists during the maintenance phase of recovery. In addition, it covers the emergency management of overdose or toxicity of medicines used to treat common mental disorders. The module on substance use disorders includes aspects of pharmacological management of dependence on nicotine, alcohol and opioids.

The manual is intended primarily to cover the use of medicines for MNS disorders in adults. However, relevant information on the use of medicines in specific age groups or populations, such as children and adolescents, older adults, pregnant and breastfeeding women and people with physical disorders, is included in each chapter. It does not include clinical assessment for diagnosis, or psychosocial interventions. Users are encouraged to refer to the mhGAP guidelines for these aspects.

The first module provides information on the basic principles of prescribing medicines for the treatment of priority MNS disorders. Subsequent modules provide practical guidelines on how to effectively manage depressive disorder, anxiety disorder, psychosis and bipolar disorder, dementia, alcohol and opioid dependence, and epilepsy, using psychotropic medicines.

Although this manual is intended for health care providers in primary health care and other non-specialist settings, reference, supervision and support from specialist mental health professionals, whenever possible, should always be considered an essential component of any treatment plan.

MODULE 1
PRINCIPLES OF PRESCRIBING

- When working with people suffering from mental, neurological and substance use (MNS) disorders, aim to foster their autonomy, promote their active participation in treatment decisions and support self-management. Make sure that discussions take place in settings in which confidentiality, privacy and dignity are respected. Take into account that stigma and discrimination are often associated with consultations for MNS disorders, which can act as a barrier to the provision of MNS services.

- As a health care provider, your relationship with individuals seeking help for MNS disorders is extremely important. Build a relationship and work in an open, engaging and non-judgemental manner. Take time to build trusting, supportive and empathic relationships as an essential part of care. Explore the person's worries in order to jointly understand the impact of the MNS disorder. Offer help, treatment and care in an atmosphere of hope and optimism. Always address commonly held beliefs that can deter people from taking medicines necessary to treat MNS disorders: for example, that people who take medicines are morally weak or that all medicines have a sedative effect.

- Your role, as a non-specialist, is extremely important in managing MNS disorders. Most of the people suffering from such disorders can be successfully treated by non-specialists. Some people may be suffering from severe or resistant disorders and may need specialist care, but many of these people also follow up with non-specialists. Therefore, it is extremely important that you are familiar with the medicines that non-specialists are allowed to prescribe (depending on local regulations) to effectively manage all priority disorders. Some of the medicines mentioned in this manual should be prescribed by specialists or under their supervision. These medicines are highlighted in each module so that you are familiar with them and can provide follow-up care where needed. You should also be familiar with the commonly available preparations of all medicines in this manual and check their availability in your own practice.

- The management of priority MNS disorders comprises both pharmacological and psychosocial interventions. Psychosocial interventions help health care providers form an alliance with persons suffering from mental disorders and their carers, which is central to a person-centred approach. The management plan for any priority MNS disorder has to be formulated in partnership with the person suffering from the disorder and their carers. The plan should be comprehensive and must address the psychological and social factors that are contributing to the disorder. The decision to prescribe a medicine does not imply that psychosocial interventions are not indicated or that psychotropic medicines are the only recommended treatment. Psychosocial interventions are beyond the scope of this manual, and you are advised to refer to the mhGAP guidelines for an overview of the management of priority MNS disorders.

- Complete a comprehensive clinical assessment and assess the associated risks. Always take a history of substance abuse, including alcohol, drugs (psychoactive) and non-medical use of prescription medicines (including psychotropic medicines). This information should be taken into account when considering the prescription of psychotropic medicines. Check the risk of suicide and be aware of any history of previous suicidal thoughts or attempts. Limit the amount of medicine prescribed and construct a regimen in which there is frequent clinical monitoring and also monitoring by family members and friends.

- Conduct a detailed physical examination, including recording weight, temperature and blood pressure. Observe carefully for signs of a physical or mental disorder, for example hyperventilation, responses to pain, facial expression and the posture of the person. Suggested monitoring also includes electrocardiogram (ECG) (mandatory in some countries for specific antipsychotics, e.g. 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, you should check for any history of cardiovascular, renal or hepatic disease and whether any medicines have been prescribed for this.

- There might be more than one medicine to treat an MNS disorder. Explore treatment options collaboratively with the person. For example, there are options for medicines to treat disorders like depression, psychosis or epilepsy. To select an appropriate medicine, consider the efficacy of past treatment, the safety profile including side-effects, cost implications, risk of overdose, drug–drug interactions and comorbidities. It is also important to check medicines prescribed for physical health conditions in people with MNS disorders. When choosing a specific medicine, consider the availability and continuity of supply. Most countries procure medicines included in the WHO Model List of Essential Medicines (EML), but if in doubt about the availability of a particular medicine consult your national formulary. In situations where continuity of supply of a medicine is likely to be interrupted, its use should be avoided.

- Exercise caution when providing medicines to special groups such as older people, those with chronic disease, women who are pregnant or breastfeeding and children/adolescents. Consult a specialist as needed. When prescribing for women of childbearing age, always check if they are pregnant. Advise them to consult you at the earliest opportunity if they become pregnant to make a decision about the safest treatment option.

- Try to involve persons suffering from MNS disorders and their carers in decisions about selecting an appropriate medicine. Educate the person about the risks and benefits of treatment, including its overall cost, potential side-effects, the duration of treatment and the importance of adherence. Inform them of possible side-effects (short- and long-term) and possible measures to manage them (e.g. a reduction in the dose), and reassure them that some of these side-effects are temporary. Encourage them to

contact you if they experience any troubling side-effects and not make any decision themselves to reduce the dose or discontinue the medicine.

- At each follow-up meeting, assess for response to treatment, side-effects of medicines and adherence to medicines and psychosocial interventions. Sometimes, persons suffering from MNS disorders might have difficulty in registering all the information about their condition and treatment. Be prepared to repeat information slowly, allowing them to ask questions or seek clarification. To check their understanding, ask them to repeat what you have explained. If needed, share additional or written information.

- You should be aware that people may hold beliefs about their illness and medicines that can influence adherence to treatment. These beliefs should be explored and you should help to dispel any myths by sharing scientific information. It is important to respect people's beliefs without making fun of them or being confrontational.

- Before prescribing any medicines, explain to the person that most medicines for MNS disorders work slowly and that they might not experience any immediate benefit. In many cases, the dose is gradually increased over weeks to reach a therapeutic level. You should also highlight the importance of taking medicines as prescribed and the need to continue treatment even after symptoms resolve to avoid relapse. Also, discontinuing abruptly can cause problems with certain medicines, so a gradual reduction is needed.

- Many people believe that all medicines used to treat mental disorders can cause dependence (addiction). While some medications can indeed play a role in developing dependence (e.g. benzodiazepines), it is important to dispel these myths and explain the chronic course of some mental disorders and the need for longer-term treatment, without the risk of dependence for most medications.

- Avoid polypharmacy (concurrent use of two or more medicines belonging to the same pharmacological class, e.g. two or more antipsychotics or two or more antidepressants). Sometimes, prescribing two medicines can have serious consequences. For example, if two antipsychotic medicines are prescribed, it increases the adverse effect burden and risks associated with QT prolongation and can cause sudden cardiac death.

- Clear documentation and recording of pharmacological interventions are extremely important, particularly in primary care settings where follow-up is likely to be provided by different health care workers.

MODULE 2
DEPRESSION

The mhGAP guidelines use the term "depression" for depressive disorder or depressive episode. The guidelines recommend that antidepressants should be considered for the treatment of moderate to severe disorder, and not for mild depression.

If sufficient resources are available, antidepressant medicine should always be offered in combination with psychological treatments, except when people prefer treatment with antidepressants only. The treatment should be offered based on individual preferences and careful consideration of the balance of benefits and harm *(1)*.

For an overview of assessment and management including psychosocial interventions, refer to the mhGAP guides (mhGAP-IG and mhGAP-HIG).

2.1 Educate the person

Before prescribing, discuss and agree a management plan with the person, which includes *(2)*:

- All options of treatment including psychological interventions (if available).
- The reasons for offering medicine.
- The choices of medicine (if a number of different antidepressants may be suitable).
- The dose, and how the dose may need to be adjusted.
- The improvements the person would like to see in their life and how the medicine may help.
- The adverse and withdrawal effects, including any side-effects that they would particularly like to avoid (e.g. weight gain, sedation, effects on sexual function).
- Any concerns they have about taking or stopping the medicine.

Discuss with the person and decide together whether to prescribe antidepressants. Explain that *(1)*:

- Antidepressants are not addictive.[1]
- It is very important to take the medicine every day as prescribed.
- Some side-effects may be experienced within the first few days but they usually resolve.
- It usually takes several weeks before improvements in mood, sleep, interest or energy are noticed.
- Educate the person on the recommended timeframe to take medicines. (Antidepressant medicines usually need to be continued for at least six months after the resolution of symptoms of a single episode, while multiple episodes may require longer.)

2.2 Select an antidepressant

Antidepressants are effective in treating people with moderate to severe depression (Table 2.1).

Even though some differences among antidepressants in terms of efficacy have been detected, these differences are of uncertain clinical significance, and therefore all antidepressants are generally considered similarly effective in the acute treatment of depressive symptoms.

However, antidepressants differ in terms of their mechanism of action and adverse effects. Selective serotonin reuptake inhibitors (SSRIs) are generally better tolerated than tricyclic antidepressants (TCAs).

Table 2.1. Classification of antidepressants

Classes	Name of the medicine	Included in EML (WHO, 2023)
Tricyclic antidepressants (TCAs)	Amitriptyline, clomipramine, dothiepin, imipramine, lofepramine, nortriptyline	Amitriptyline
Selective serotonin reuptake inhibitors (SSRIs)	Fluoxetine, citalopram, escitalopram, paroxetine, sertraline, fluvoxamine	Fluoxetine Therapeutic alternatives: – citalopram – escitalopram – fluvoxamine – paroxetine – sertraline
*Serotonin norepinephrine reuptake inhibitors (SNRIs)	Duloxetine, venlafaxine	
*Other antidepressants	Mirtazapine, trazadone	

*The mhGAP guidelines do not recommend prescribing these medicines in primary care, but non-specialists might still need to follow up people who have been prescribed them by mental health specialists.

[1] Although "discontinuation symptoms" are reported when some antidepressant medicines are stopped, these are not the same as "withdrawal symptoms". The difference between discontinuation and withdrawal symptoms is that the latter implies addiction, while the former does not. Addiction is characterized by compulsive drug-seeking behaviour, despite negative consequences. Withdrawal symptoms can be explained in the context of "receptor rebound"; for example, an antidepressant with potent anticholinergic side-effects may be associated with diarrhoea on discontinuation *(3)*.

An antidepressant should be carefully selected based on the individual person's needs and preferences. SSRIs are generally well tolerated, have a good safety profile and are generally considered as the first choice for most people.

To select an antidepressant, consider:

- The availability of the drug in your health care facility and geographic location (guided by the WHO EML, which includes the most efficacious, safe and cost-effective medicines).
- The person's age (e.g. avoid amitriptyline in older adults with cardiac problems).
- The side-effect profile of the drug.
- The risk of overdose (avoid TCAs, such as amitriptyline, in people at risk of self-harm).
- Concurrent medical conditions: for example, if a person suffers from specific medical problems, some agents might be better avoided (e.g. venlafaxine should be prescribed cautiously in the case of individuals with high blood pressure).
- Past history or response/non-response to the antidepressant: for example, if a person has responded well, without intolerable side-effects, to a specific agent, that agent might be chosen; if a person has failed to respond, or has had intolerable side-effects, to a specific agent, that agent should generally no longer be prescribed.
- The affordability of the medicine and cost implications.

2.3 Initiate treatment

Initiate medicine only if the person agrees to pharmacological treatment. Start with only one medicine at the lowest dose and gradually increase to the target dose over a period of 7–14 days (Table 2.2) *(1)*.

Table 2.2. Dosage regimen

	Medicine	Starting dose	Maximum dose
TCA	Amitriptyline	Start 25 mg at bedtime	Increase by 25–50 mg per week Minimum treatment dose: 75 mg per day Maximum dose: 150 mg per day For older adults: maximum dose: 100 mg per day
SSRI	Fluoxetine	Start 10 mg daily for one week, then 20 mg daily	20 mg per day If no response in six weeks, increase to 40 mg (maximum 80 mg) For adolescents and older adults: maximum dose: 40 mg per day

Once an antidepressant has been selected, the person should be reviewed after two weeks *(3)*.

Initially maintain contact frequently, e.g. monthly, for the first three months *(1)*. If the person is recovering, reduce the frequency of contact.

During follow-up visits, the person should be asked about drug tolerability and side-effects, with adjustment of the dose if necessary. Adherence to medicines, mood symptoms and suicide risk need to be monitored *(1)*. It is also important to assess for any emergent symptoms of mania, particularly in people with a history of previous episodes and a family history of bipolar disorder *(1)*.

TCAs are generally associated with higher rates of adverse effects than SSRIs (Table 2.3).

Table 2.3. Side-effects *(1)*

Class of antidepressant	Common side-effects	Serious side-effects	Cautions *(see section 2.7 for special populations)*
TCAs	Sedation, constipation, dryness of mouth, orthostatic hypotension (risk of fall), blurred vision, difficulty urinating, nausea, weight gain, sexual dysfunction	ECG changes (e.g. QTc prolongation), cardiac arrhythmia, increased risk of seizure	Avoid in persons with cardiac disease, history of seizure, hyperthyroidism, urinary retention or narrow-angle glaucoma, prostatism and bipolar disorder (can trigger mania in people with untreated bipolar disorder) May increase suicidal ideation in young adults
SSRIs	Insomnia, headache, dizziness, gastrointestinal disturbances, changes in appetite, sexual dysfunction	Bleeding abnormalities in those who use aspirin or other nonsteroidal anti-inflammatory drugs, low sodium levels	Caution in persons with history of seizure May increase suicidal ideation in young adults
Selective serotonin noradrenaline reuptake inhibitors (SNRIs)	Nausea, headache, insomnia, somnolence, dry mouth, dizziness, sexual dysfunction In persons taking venlafaxine, blood pressure should be regularly checked	Elevation of blood pressure at high doses Monitor for signs and symptoms of cardiac dysfunction, particularly in those with known cardiovascular disease	Caution in persons with history of seizure

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

Both depression and the medicines used to treat it can cause disorders of sexual desire, arousal and orgasm. Although many individuals experience treatment-emergent sexual dysfunction while taking antidepressants, in others the reduction in depressive symptoms can be accompanied by improvements in sexual desire and satisfaction. Sexual dysfunction with antidepressants is likely to be dose-dependent and is generally considered to be fully reversible. However, there have been reports of long-lasting sexual dysfunction where the symptoms have continued despite the discontinuation of SSRIs. The term "post-SSRI sexual dysfunction" (PSSD) has been used to describe these symptoms. The prevalence and pathophysiology of PSSD remain uncertain *(3)*.

Sexual side-effects can be minimized by careful selection of antidepressant drug. The prevalence of sexual dysfunction induced by TCAs is around half of that induced by SSRIs, and the antidepressant mirtazapine causes less sexual dysfunction than SSRIs *(3)*. Dose reduction can also be considered in individuals who have achieved full remission on an antidepressant *(3)*.

Do not combine antidepressants, as this may cause serotonin syndrome (Table 2.4). This can occur in the context of the initiation or increase in dose of a serotonergic agent, more frequently in the combination of serotonergic drugs. It is characterized by altered mental state, agitation, tremor, shivering, diarrhoea, hyperreflexia, myoclonus, ataxia and hyperthermia.

To manage serotonin syndrome *(4)*:

1. Discontinue the serotonergic medication.
2. Provide supportive care, including:
   - Administration of oxygen.
   - Intravenous fluids.
   - Continuous cardiac monitoring.
   - Correction of vital signs.
3. For sedation, use diazepam 10 mg intravenously. This can be repeated if needed.

Table 2.4. Serotonin syndrome *(3)*

Mild	Insomnia, anxiety, nausea, diarrhoea, hypertension, tachycardia, hyperreflexia
Moderate	Agitation, myoclonus, tremor, mydriasis, flushing, diaphoresis, low fever (< 38.5 °C)
Severe	Severe hyperthermia, confusion, rigidity, respiratory failure, coma, death

2.4 Monitor treatment

Treatment should be regularly monitored, with special attention to treatment adherence, changes in depressive symptoms and possible adverse effects.

Antidepressants may take up to 4–6 weeks to have a therapeutic effect *(2)*.

If the symptoms are improving after 4–6 weeks, continue the treatment. Follow up every 2–4 weeks until the person fully recovers. When the person completely recovers after the first episode of depressive disorder, continue the medicine for at least six months after recovery.

If there is no response after 4–6 weeks, consider changing the medicine to a different class.

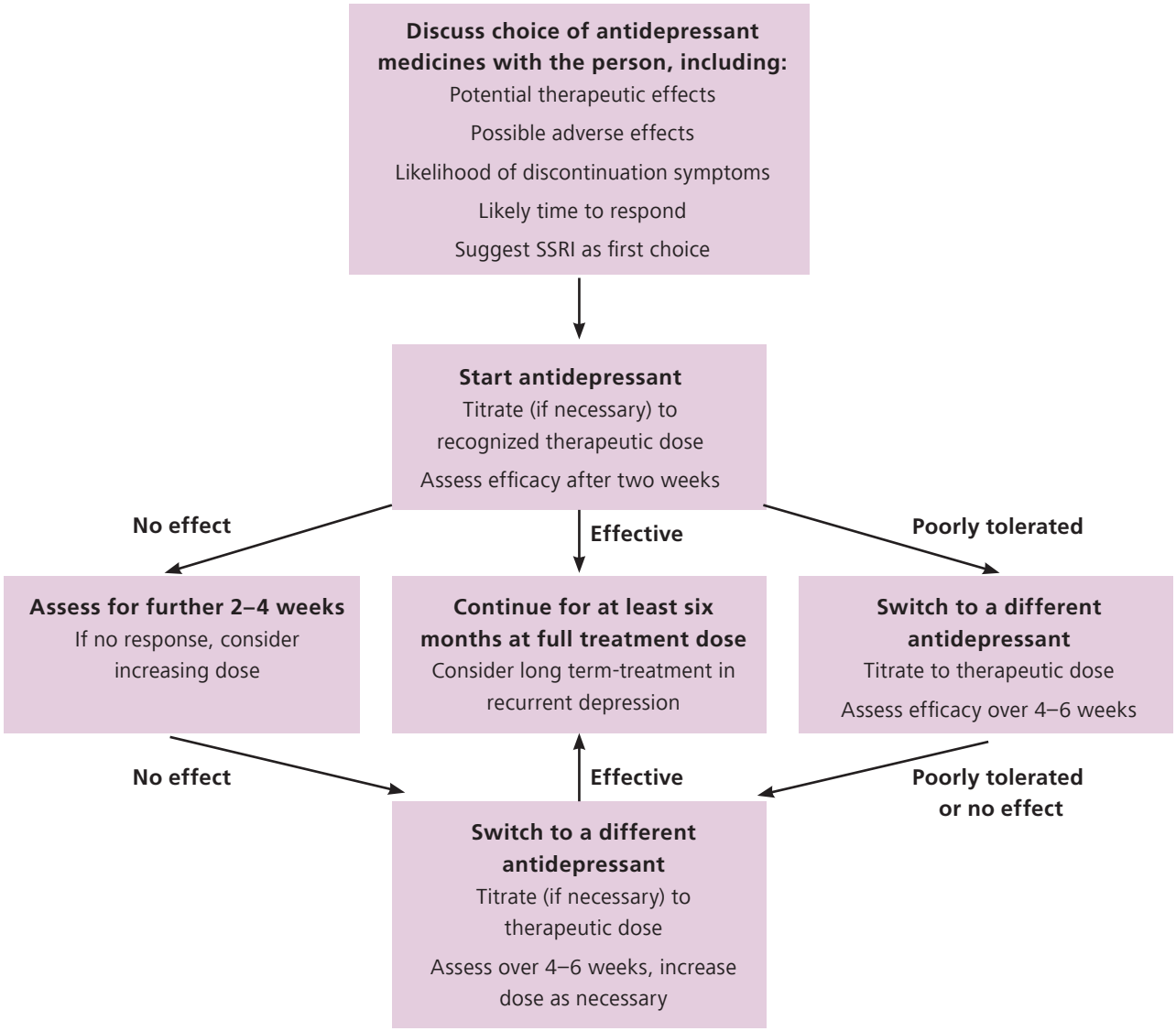
If there are problems in tolerating the treatment, consider changing to another antidepressant. Gradually reduce the dose of the first antidepressant and gradually increase the dose of the new antidepressant. Switch from one antidepressant to another with caution, particularly with fluoxetine because of its long half-life. For example, if switching from fluoxetine to another SSRI or an SNRI, wait for 4–7 days after stopping fluoxetine and before starting the new antidepressant *(3)*.

For adults under 30 years of age who are prescribed antidepressants:

- Inform them of increased risk of suicidal thinking and self-harm behaviour among younger people when taking these medicines.
- Ensure follow-up within one week after initiating the medicines.
- Monitor and follow up on suicidal thinking and self-harm on a regular (e.g. weekly) basis within the first month after initiating the medicine or changing the dose *(1)*.

Follow the steps in Figure 2.1 to monitor the efficacy of antidepressant treatment *(3)*.

Figure 2.1. Monitoring the efficacy of antidepressant treatment



Refer to a specialist if *(1)*:

- Depression presents with psychotic symptoms such as delusions or hallucinations.
- There is imminent risk of suicide (e.g. the person has recently attempted suicide).
- There is a history of untreated acute or chronic physical illness or recent head injury.
- There is gross memory impairment and disorientation.
- There is no or limited response to at least two sequential treatments with antidepressants in adequate dose and duration.
- In children and adolescents when psychosocial interventions are not effective.
- In pregnant or breastfeeding women.

2.5 When and how to stop medicine

Medicines should never be stopped just because the person experiences some improvement.

For adult individuals with depressive episode/disorders who benefit from initial antidepressant treatment, the antidepressant treatment should not be stopped before six months after remission. Treatment (on the same dose) should be regularly monitored, with special attention to treatment adherence *(3)*.

Frequency of contact should be determined by adherence, severity, progress and by local feasibility issues.

If depressive symptoms relapse:

- Check compliance.
- Explore other sources of distress.
- Check physical health.
- Explore substance use.
- Consider the possibility of adjusting the dosage (if not already on the highest dose).

If symptoms get worse, consider a change of medicine.

When stopping antidepressant medicine, agree on a plan with the person to reduce the dose. If possible, do this in a stepwise fashion, e.g. reduce to half of previous dose. Consider even smaller reductions, if possible. Antidepressants with a short half-life will need to be tapered more slowly.

Some commonly used antidepressants such as paroxetine and venlafaxine are more likely to be associated with discontinuation symptoms (Table 2.5). These are mostly mild, may appear within a few days of reducing or stopping the antidepressant medicine and usually go away within 1–2 weeks. Sometimes the symptoms may last longer (up to several weeks) *(3)*. Owing to the long half-life of fluoxetine, withdrawal symptoms can be delayed by weeks, and so careful attention should be paid to this. As the withdrawal period is spread out over a longer period, larger reductions of fluoxetine may be relatively tolerable *(3)*.

Table 2.5. Discontinuation symptoms *(3)*

Sensory symptoms	Numbness, shock-like sensations, altered taste/smell/vision
Affective symptoms	Anxiety, agitation, irritability, panic attacks
General somatic symptoms	Flu-like symptoms, headache, sweating, anorexia, tachycardia
Disequilibrium	Dizziness (most common), vertigo, light-headedness
Sleep symptoms	Insomnia, nightmares, excessive dreaming
Gastrointestinal	Nausea, vomiting, diarrhoea
Cognitive	Confusion, decreased concentration

2.6 Prevent risk of overdose

When prescribing antidepressant medicine for people at risk of suicide, take into account toxicity in overdose. SSRIs are the first choice. An overdose of TCAs such as amitriptyline (around 500 mg *(3)*) may be fatal and therefore should be avoided in this group.

- Be aware that the risk can increase in the early stages of antidepressant treatment.
- Review the person weekly after starting the antidepressant medicine, and assess their support system and psychosocial stressors.
- Give them a limited supply of antidepressants (e.g. one week's supply at a time).
- Ask the person's carers to keep and monitor medicines and to follow up frequently to prevent an overdose of medicine.
- Be aware that the risk from overdose increases when used with other medicines and alcohol.

If overdose of an antidepressant is suspected, referral to an acute medical facility is recommended *(1)*.

The treatment for TCA overdose includes the following *(5)*:

- Look for clinical features of TCA overdose (Table 2.6). These include dilated pupils, dry mouth, drowsiness, sinus tachycardia, urinary retention, increased tendon reflexes and extensor plantar responses.
- Do not try to induce vomiting. Gastrointestinal decontamination by activated charcoal should be done only if conditions are appropriate and the airway is protected. Charcoal decontamination may be effective only up to two hours post-ingestion.
- Seizures usually respond to benzodiazepines, but in cases of refractory seizures prompt administration of antiseizure medicines, such as phenobarbital, may be required.
- Sodium bicarbonate should be given if the QRS prolongation is of more than 100 milliseconds. It is the mainstay for treatment of cardiovascular effects of TCA overdose. Sodium bicarbonate is given as a bolus of 1 mEq/kg intravenously, followed by an intravenous infusion containing sodium bicarbonate.

Table 2.6. Clinical features of overdose of antidepressant medicine *(3)*

Medicine	Clinical features
TCAs	Sedation, hypotension, tachycardia, ECG 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
SSRIs	Vomiting, tremor, drowsiness, tachycardia, ECG changes, convulsions At high doses decreased consciousness may occur Very rarely results in fatality
Venlafaxine	Sedation, tachycardia, ECG changes, convulsions Large amounts may lead to fatality

Note: antidepressant overdose in combination with alcohol or other medicines appears to be associated with increased toxicity.

2.7 Special populations

Children and adolescents

In children and adolescents, if symptoms persist or worsen despite psychosocial interventions, refer to a specialist.

In adolescents over 12 years of age, if symptoms persist or worsen despite psychosocial interventions, consider fluoxetine (under supervision of a specialist). If fluoxetine is prescribed, ask the adolescent to return weekly, for the first four weeks, to monitor thoughts or plans of suicide and any potential adverse effects *(1)*.

Pregnant and breastfeeding women

If possible, avoid antidepressant medication in pregnancy or breastfeeding. Consider medication at the lowest effective dose if there is no response to psychosocial interventions. It is best to consult a specialist, if available *(1)*.

If drug treatment is required in women who are planning a pregnancy or are pregnant, previous response must be taken into account. For previously untreated patients, sertraline may be considered *(3)*.

If the woman is breastfeeding, avoid long-acting antidepressant medicine such as fluoxetine. Sertraline or mirtazapine may be considered *(3)*.

Older adults

Start with a low dose and increase slowly, but do not undertreat.

Keep therapy simple i.e. once-daily administration.

Avoid, if possible, TCAs drugs including amitriptyline that block α1 adrenoceptors, have anticholinergic adverse effects and are sedative. TCAs have a higher risk of orthostatic hypotension and falls.

SSRIs are a better choice but increase the risk of gastrointestinal/other bleeds and risk causing hyponatraemia *(3)*.

Hepatic impairment

SSRIs are the preferred choice. Prescribe at a lower starting dose, with longer intervals between increases in dosage. Sedative TCAs such as amitriptyline are best avoided *(3)*.

Renal impairment

Fluoxetine may be needed on alternate days in severe renal impairment.

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MODULE 3
ANXIETY DISORDERS

In the context of the mhGAP guidelines, the term "anxiety disorders" includes generalized anxiety disorder and panic disorder only.

If sufficient resources are available, antidepressant medicine should always be offered in combination with psychological treatments for anxiety disorders, except when people prefer treatment with antidepressants only. The treatment should be offered based on individual preferences and careful consideration of the balance of benefits and harm *(1)*.

3.1 Educate the person

Please refer to section 2.1.

In addition, explain the risk of dependence with benzodiazepines, if prescribed.

3.2 Start and monitor treatment

Consider SSRIs for adults with generalized anxiety disorder or panic disorder as these are generally better tolerated than TCAs. Where SSRIs are not available, consider TCAs for adults with panic disorder only *(2)*.

SSRIs should initially be prescribed at half the normal dose and gradually increased as tolerated. Initial worsening of anxiety may be seen when treatment is started *(3)*. Reassure the person that this may resolve spontaneously. SSRIs may take longer to work for anxiety. Modest benefit is usually seen within six weeks and will continue to increase over time *(3)*.

- Review the effectiveness and side-effects of the drug every 2–4 weeks during the first three months of treatment and every three months thereafter, particularly at 12 months. If the drug is effective, advise the person to continue taking it for at least six months, as the likelihood of relapse is high following early discontinuation.
- For people who develop side-effects that they find tolerable, provide information and monitor the symptoms closely. If side-effects are not tolerable, reduce the dose of the drug or stop it, according to the person's preference. Offer an alternative medicine (another SSRI or TCA for panic disorder). If the alternative medicine is not tolerated or does not improve symptoms, refer to a specialist.
- For further details on doses, side-effects and cautions of TCAs and SSRIs, see sections 2.3 and 2.7.

3.3 Short-term treatment with benzodiazepines

The main objective of treatment with benzodiazepines (Table 3.1) is to reduce severe and disabling symptoms of anxiety rapidly so that an antidepressant or psychosocial intervention can be initiated.

In view of the risk of dependence, benzodiazepine for the treatment of anxiety disorder in primary care should be prescribed for acute anxiety and as a short-term (3–7 days maximum) measure ONLY *(3)*.

Table 3.1. Classification of benzodiazepines *(3)*

Long half-life	Intermediate half-life	Short/ultra-short half-life
Diazepam (EML)	Bromazepam	Oxazepam
Chlordiazepoxide	Temazepam	Lorazepam
Flurazepam	Alprazolam	Triazolam
Nitrazepam		

- 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 1–3 times daily, up to oral doses of 5–10 mg per day (Table 3.2).

Table 3.2. Prescribing diazepam *(3)*

Dosage	Common side-effects	Serious side-effects
Adults: 2 mg three times a day, then increased if necessary to 15–30 mg daily in divided doses Older adults: 1 mg three times a day, then increased if necessary to 7.5–15 mg daily in divided doses	Drowsiness, sedation, muscle weakness Diazepam can adversely affect parameters of driving performance in healthy subjects	Vertigo, headache, confusion, depression, dysarthria, changes in libido, tremor, visual disturbances, urinary retention or incontinence, gastrointestinal disturbances, changes in salivation, amnesia Some individuals may experience a paradoxical excitation which may lead to hostility, aggression and disinhibition Rarely, jaundice, blood disorders and hypersensitivity reactions Respiratory depression and hypotension occasionally occur with high dosage and parenteral administration

Risk of dependence

Prolonged use of benzodiazepines can lead to memory impairment, increased risk of falls in the elderly, risk of fatal sedative overdose, development of tolerance, withdrawal syndrome and dependence.

Prolonged use leading to dependence is likely to happen because:

- Of the past practice trend to prescribe benzodiazepines for anxiety for a longer period of time. As a result, there are many people in the community who are dependent on these medicines.
- Benzodiazepines are sometimes prescribed by health care providers for conditions other than acute anxiety (whereas they should be used for 3–7 days only).
- In the absence of regulation in many countries, people can buy these medicines from pharmacies without a prescription.

Non-specialists should also be aware of the risk of diversion (i.e. persons selling benzodiazepines to others).

3.4 Withdrawing benzodiazepines

Benzodiazepines can only be tapered off if a person is willing to do so. Engage the person well before planning to withdraw the medication. It should not be imposed on a person against their will. Offer support to prepare a person for withdrawal and through the process. Do not blame the person for their dependence on benzodiazepines.

Withdrawal symptoms can be troubling and the reduction has to be very gradual. Sudden benzodiazepine withdrawal may have severe or life-threatening consequences (Table 3.3). If severe uncontrolled benzodiazepine withdrawal develops or occurs due to a sudden or unplanned cessation, consult a specialist and hospitalize the person *(1)*.

Table 3.3. Withdrawal effects from benzodiazepines *(3)*

Psychological symptoms	Physical symptoms
Anxiety/insomnia	Stiffness
Terror/panic attacks	Fatigue and weakness
Nightmares	Gastrointestinal disturbance
Depersonalization (experiencing the self as strange or unreal)	Paraesthesia
Derealization (experiencing the world as strange or unreal)	Flu-like symptoms
Cognitive impairment	Visual disturbances
Impaired memory	Sensory hypersensitivity
Delusions and hallucinations	Tremor
Depression	Dizziness
Psychosis	Muscle spasms/cramps
Mood instability	Hypertension
Paranoia	Tachycardia
Obsessive-compulsive symptoms	Delirium
Suicidal ideation	Convulsions
Mania	

Benzodiazepines should be gradually tapered over 8–12 weeks, depending on the daily dosage, and in conjunction with psychosocial support. More rapid tapering is possible only if the person is in an inpatient setting in a hospital or detoxification facility *(4)*.

Individuals who take short- or intermediate-acting benzodiazepines can be tapered off directly, but dosing of more than once a day might be required. Usually a 10% reduction in the total dose every 2–4 weeks is tolerable, although some long-term users may need even slower reductions.

Final doses before complete cessation will need to be very small (often much less than 1 mg of diazepam equivalent) *(3)*. If significant withdrawal symptoms emerge at any point, either hold the current dose to allow them to resolve or, if intolerable, increase to the last dose at which the symptoms were tolerable and remain there until symptoms resolve.

An alternative approach is to switch to an equivalent dose of diazepam (Table 3.4), which has a long half-life and therefore might provoke less severe withdrawal.

Table 3.4. Doses (approximately) equivalent to diazepam 10 mg *(3)*

Chlordiazepoxide	25 mg
Clonazepam	0.5 mg
Lorazepam	1 mg
Nitrazepam	10 mg
Oxazepam	20 mg
Temazepam	20 mg

Once the person is stable, tapering will need to be more gradual, with reduction in smaller amounts and/or longer periods between reductions.

The experience of distressing withdrawal symptoms does not indicate that a person cannot stop benzodiazepines but that they will need to taper more slowly, with smaller reductions than they have been undertaking (some need to taper at less than 5% of the most recent dose per month) *(3)*.

3.5 Overdosage of benzodiazepines

Benzodiazepines as a group have a low risk of toxicity. The outcome of benzodiazepine overdoses is generally less life-threatening unless alcohol or certain medicines, such as antipsychotics or antidepressants, have been ingested. Isolated benzodiazepine overdose may present with central nervous system depression with normal or near-normal vital signs. Symptoms include slurred speech, ataxia and altered mental status. If taken with other agents such as ethanol, respiratory depression may be noted.

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

There is an antidote, flumazenil, which is a nonspecific competitive antagonist at the benzodiazepine receptor that can reverse benzodiazepine-induced sedation. However, in most cases, the risks of flumazenil usually outweigh the benefits in acute toxicity, and thus flumazenil is not recommended for routine reversal of this sedative agent *(4)*.

In primary care, only supportive care should be provided, including intravenous fluids administered to manage haemodynamic instability.

3.6 Special populations

Pregnant and breastfeeding women

Avoid benzodiazepines in pregnancy as their use is associated with congenital malformations in the infant when used during the first trimester. They may also be associated with neonatal withdrawal symptoms (floppy infant syndrome) if used in the third trimester. However, in cases of managing alcohol withdrawal in pregnant women, benzodiazepines can be lifesaving (see sections 6.2 and 6.5).

For managing benzodiazepine withdrawal in pregnant women, inpatient care should be considered. A gradual dose reduction using long-acting benzodiazepines (for the shortest possible period) should be offered. Psychosocial interventions should be offered throughout the period of benzodiazepine withdrawal.

Avoid during lactation; however, if needed, use benzodiazepines with a short half-life, such as lorazepam and oxazepam.

Older adults

Avoid in older adults; however, if needed, use benzodiazepines with a short half-life, such as lorazepam nd oxazepam.

Renal or hepatic impairment

Avoid when liver or kidney function are impaired; however, if needed, use benzodiazepines with a short half-life, such as lorazepam and oxazepam.

Respiratory insufficiency

Do not use benzodiazepines in cases of respiratory failure.

Children and adolescents

Avoid benzodiazepines in children and adolescents.

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MODULE 4
PSYCHOSES

The mhGAP guidelines use "psychoses" as a broad category which encompasses psychotic disorders (including schizophrenia) and bipolar disorders *(1)*.

People living with psychoses should be involved in medicine choice in a supported decision-making process, without coercion. Treatment with antipsychotic medicines should be combined with psychosocial interventions.

For an overview of assessment and management including psychosocial interventions, refer to the mhGAP guides (mhGAP-IG and mhGAP-HIG).

4.1 Educate the person/carers

- Explain that the symptoms are due to a mental health condition, that psychosis and bipolar disorders can be treated and that the person can recover.
- Do not blame the person or their family or accuse them of being the cause of the symptoms.
- Address any myths or misconceptions e.g. that symptoms are due to witchcraft or being possessed.
- Educate the person and the family that the person needs to take an antipsychotic medicine regularly, as prescribed *(1)*.
- Advise them about maintaining a healthy lifestyle, e.g. a balanced diet, physical activity, regular sleep, good personal hygiene and no stressors. Stress can worsen psychotic symptoms *(1)*.
- Explain that the medicine is started at a low dose and titrated slowly to reduce the risk of side-effects *(2)*.
- Emphasize the need for regular monitoring and follow-up.
- Recommend avoiding alcohol, cannabis or other nonprescription drugs, as they can worsen psychotic or bipolar symptoms *(3)*.

4.2 Psychotic disorders (including schizophrenia)

Antipsychotic medicines are the primary medicine for schizophrenia and related psychotic disorders. These agents are particularly effective against acute psychotic symptoms such as hallucinations, delusions, agitation, and disorganized thought and behaviour *(2)*.

4.2.1 Select an antipsychotic medicine

Antipsychotic medicines are classified into conventional or first-generation and atypical or second-generation antipsychotic medicines (Table 4.1).

Table 4.1. Classification of antipsychotic medicines *(1)*

First-generation antipsychotics	Chlorpromazine Haloperidol Fluphenazine
Second-generation antipsychotics	Risperidone Paliperidone Olanzapine Aripiprazole Quetiapine *Clozapine

*Clozapine should be considered for adults with a treatment-resistant psychotic disorder (including schizophrenia) under mental health specialist supervision, carefully balancing effectiveness and side-effects *(1)*.

All antipsychotic medicines (with the exception of clozapine) are considered similarly effective but they differ in side-effect profile. The choice of drug should be made in consultation with the person and their carers, considering *(2):*

1. Availability of the drug (potential interference with reliable supply for the continuation of treatment should inform the choice of medicine).

2. Side-effect profile:

- Metabolic (including weight gain and diabetes).
- Extrapyramidal (including akathisia, dyskinesia and dystonia).
- Cardiovascular (including prolonging the QT interval).
- Hormonal (including increasing plasma prolactin).
- Other (including unpleasant subjective experiences).

3. Past history of antipsychotic responsiveness.

If a person has already responded well, without intolerable side-effects, to a specific medicine, consider the same medicine. Similarly, if a person has failed to respond, or has had intolerable side-effects, to a specific medicine, do not prescribe it again.

4. Cost implications for the person and carers.

5. Treatment adherence.

6. Medical comorbidities.

If a person suffers from specific medical problems, some medicines should be avoided e.g. haloperidol should be avoided in older adults with ECG abnormalities; olanzapine and clozapine should be prescribed cautiously to people with abnormalities of glucose control.

4.2.2 Initiate treatment

Consider antipsychotic medicine immediately after diagnosing psychosis. Before starting the medicine, check:

- Weight and blood pressure.
- ECG.
- Full blood count.
- Serum urea, electrolytes and creatine phosphokinase.
- Liver function tests.
- Blood glucose.
- Lipid profile.
- Serum prolactin.

If laboratory tests are not feasible, at least check for a history of cardiovascular, renal or hepatic disease before prescribing. However, laboratory tests are essential if clozapine is to be prescribed *(3)*.

Start at the lowest dose and gradually increase to reduce the risk of side-effects (Table 4.2). The minimum effective dosage should be prescribed. Higher doses of antipsychotics increase the risk of adverse reactions without providing additional benefit. Try the medication at a typically effective dose for at least 4–6 weeks before considering it ineffective.

For older adults, use lower doses of medicine (one half to one third the adult dose is recommended).

If there is risk of harm to self or others, refer to a specialist.

Table 4.2. Dosage of antipsychotic medicines

Medicine	Minimum effective dose	Route	Maximum dose
Haloperidol *(1)*	Start 1.5–3 mg per day Increase as needed	Oral Can be used intramuscularly, if needed	20 mg per day
Risperidone *(1)*	Start 1 mg per day Increase to 2–6 mg per day	Oral	10 mg per day
Chlorpromazine *(1)*	Start 25–50 mg per day Increase to 75–300 mg/day	Oral	Up to 1000 mg (for severe cases)
Paliperidone *(2)*	3 mg per day	Oral	12 mg per day
Aripiprazole *(2)*	10 mg per day	Oral	30 mg per day
Olanzapine *(2)*	5 mg per day	Oral	20 mg per day
Quetiapine *(2)*	150 mg per day	Oral	750 mg per day for schizophrenia; 800 mg per day for bipolar disorder
Clozapine *(2)* *(see section 4.2.5 for further details)*	300–450 mg per day	Oral	900 mg per day
Long-acting antipsychotic injections			
Fluphenazine depot/ long-acting *(1)*	Start with 12.5 mg (a test dose) and wait for seven days; then use 12.5–50 mg every 2–4 weeks	Intramuscular (gluteal region)	
Paliperidone long-acting *(2)*	50 mg per month	Intramuscular (deltoid or gluteal region)	150 mg per month
Risperidone long-acting *(2)*	25 mg every two weeks	Intramuscular (deltoid or gluteal region)	50 mg every two weeks
Haloperidol *(2)*	50 mg every four weeks	Intramuscular (gluteal region)	300 mg every four weeks
Zuclopenthixol *(2)*	200 mg every three weeks	Intramuscular (gluteal region or thigh)	600 mg per week

4.2.3 Monitor treatment

Monitor and record the following regularly throughout treatment:

1. Response to treatment, including changes in symptoms and behaviour.

2. Side-effects of treatment (Table 4.3):

- If the person is not tolerating the medicine, consider reducing the dose.
- If adverse reactions persist despite a reduction in dose, a switch to another antipsychotic may be considered *(2)*.
- Consider anticholinergic medicine for short-term use to treat extrapyramidal symptoms (EPS) if these strategies fail or if symptoms are severe.

3. Adherence to treatment.

If treatment adherence is a major problem, involve the person and family members:

- Provide information regarding the importance of medication.
- Discuss reasons for non-adherence.
- Check side-effects (see above).
- Consider the possibility of switching to a long-acting preparation after consultation with the person and their family.
- In the case of risperidone long-acting injections, the response is usually delayed for 2–3 weeks. Oral treatment may be required during this phase *(2)*.
- Please note that no treatment, particularly long-acting treatments, should be given by non-specialists without the consent of the person. If the person refuses treatment, the immediate aim should be to consult or refer to a specialist.

4. Monitor overall physical health.

Check the following every 12 weeks for one year, and then annually *(3)*:

- Weight/body mass index (BMI).
- Pulse and blood pressure.
- Fasting blood glucose or HbA1c.
- Blood lipid levels.

5. Treatment response.

If no improvement in symptoms is seen after 4–6 weeks:

- Ensure that the dose is adequate; if not, increase gradually.
- Enquire about alcohol or substance use and take measures to reduce this.
- Explore recent stress.
- Switch to another oral antipsychotic *(1)*. 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 one.
- If antipsychotic combination or clozapine is needed, it should be carefully monitored under specialist supervision.

Table 4.3. Types of side-effects of antipsychotics *(2)*

Neurological	Extrapyramidal symptoms (EPS) (includes parkinsonian effects, akathisia, acute dystonia, tardive dyskinesia) and neuroleptic malignant syndrome (NMS)
Anticholinergic	Peripheral (dry mouth, blurred vision, constipation, urinary retention) and central effects of the cholinergic system (severe agitation and confusion)
Metabolic	Weight gain, hyperglycaemia, ketoacidosis, diabetes and lipid dysregulation
Other miscellaneous	Sedation, ECG abnormalities, orthostatic hypotension, increased prolactin resulting in gynecomastia, galactorrhoea, amenorrhoea, impotence, leukopenia, agranulocytosis, jaundice, elevated liver enzymes, photosensitivity, skin eruptions, retinal pigmentation

4.2.4 Individual antipsychotic medicines

Table 4.4. Side-effects of antipsychotic medicines

Side-effects of first-generation antipsychotic medicines *(1)*			
Medicine	**Common side-effects**	**Serious side-effects**	**Contraindications/cautions** *(see section 4.2.9 for special populations)*
Haloperidol	Sedation, dizziness, blurred vision, dry mouth, urinary retention, constipation	Orthostatic hypotension, EPS, ECG changes (prolonged QT interval), weight gain, galactorrhoea, amenorrhoea, NMS	Caution in persons with kidney disease, liver disease, cardiac disease, long QT syndrome or taking QT-prolonging medicines Monitor ECG if possible
Chlorpromazine	Sedation, dizziness, blurred vision, dry mouth, urinary retention, constipation, tachycardia	Orthostatic hypotension, syncope, EPS, photosensitivity, weight gain, galactorrhoea, amenorrhea, sexual dysfunction, priapism, NMS, agranulocytosis, jaundice	Contraindications: impaired consciousness, bone marrow depression, pheochromocytoma Caution in persons with respiratory disease, kidney disease, liver disease, glaucoma, urinary retention, cardiac disease, long QT syndrome or taking QT-prolonging medicines. Monitor ECG if possible
Zuclopenthixol *(4)*	Dry mouth, blurred vision, constipation, nausea, difficulty in micturition	Orthostatic hypotension, EPS, galactorrhoea, amenorrhoea, NMS	Caution in persons with cardiac disease, kidney disease, glaucoma or liver disease
Fluphenazine depot/long-acting	Sedation, dizziness, blurred vision, dry mouth, urinary retention, constipation, tachycardia, amenorrhoea, sexual dysfunction, NMS	Orthostatic hypotension, syncope, EPS, photosensitivity, weight gain, galactorrhoea	Contraindications: impaired consciousness, parkinsonism Caution in persons with cardiac disease, kidney disease or liver disease
Side-effects of second-generation antipsychotic medicines			
Risperidone *(2)*	Sedation, dizziness, tachycardia	Orthostatic hypotension, metabolic effects (elevated lipids, insulin resistance, weight gain), EPS, elevated prolactin, sexual dysfunction, amenorrhoea, gynecomastia, NMS	Caution in persons with cardiac disease, persons with known hypersensitivity to phenothiazines, situations where a large amount of central nervous system depressant is present (such as alcohol or benzodiazepines)
Olanzapine *(2)*	Weight gain, fatigue, dizziness, sedation *(3)*	Hyperglycaemia, ketoacidosis, diabetes, lipid dysregulation (which are risk factors for cardiovascular morbidity and mortality	Caution in persons with diabetes
Quetiapine *(2)*	Somnolence, dizziness, constipation	Postural hypotension	Caution in persons with cardiac disease
Paliperidone *(4)*	Tachycardia, somnolence, akathisia, dystonia, EPS, parkinsonism	Orthostatic hypotension, sexual dysfunction, raised prolactin levels	Caution in persons with renal impairment or cardiac disease

Aripiprazole *(4)*	Anxiety, constipation, dizziness, headache, insomnia, nausea, vomiting	Akathisia	Caution in persons with seizures
Clozapine *(2)*	Sedation, constipation, hypersalivation, hypotension, tachycardia, weight gain, increased blood sugars	Agranulocytosis (risk of fatal agranulocytosis is around 10 times higher with clozapine than with other antipsychotics), myocarditis, cardiomyopathy, pulmonary embolism	Caution in persons with diabetes or seizures Risk of agranulocytosis *(see section 4.2.5 for regular monitoring of white blood cell count)*

If parkinsonian effects develop, reduce the dose of the antipsychotic.

If parkinsonian effects persist despite the decrease in dose, consider antiparkinsonian agents, such as biperiden 2–4 mg per day (Table 4.5).

For acute dystonia, and if a person is unable to swallow because of muscle spasms, then intramuscular anticholinergic is the treatment of choice. The response to intramuscular administration takes around 20 minutes. It is better to avoid intravenous administration in non-specialized settings *(2)*.

Table 4.5. Antiparkinsonian medicine *(1)*

Medicine	Dosage	Common side-effects	Contraindications/ cautions
Biperiden	Start 1 mg twiceper day orally Increase to 3–12 mg daily Can also be used intravenously	Sedation, confusion and memory disturbance (especially in older adults), tachycardia, dry mouth, urinary retention, constipation Rarely, angle-closure glaucoma, myasthenia gravis and gastrointestinal obstruction	Caution in persons with cardiac disease, liver disease or kidney disease Caution when combining with other anticholinergic medicines
Trihexyphenidyl (benzhexol)	Start 1 mg per day orally Increase to 4–12 mg per day in 3–4 divided doses (maximum 20 mg daily)		

Neuroleptic malignant syndrome (NMS) occurs as a rare but serious adverse effect of antipsychotics, which is potentially fatal if untreated *(2)*. NMS is an acute disorder which is characterized by muscular rigidity, hyperthermia, altered consciousness and autonomic dysfunction, following exposure to antipsychotic medicine. The clinical features may include fever, diaphoresis, rigidity, confusion, fluctuating levels of consciousness, fluctuating blood pressure, tachycardia, elevated creatine kinase levels, leukocytosis and altered liver function tests.

NMS is an acute medical emergency. If suspected, immediately stop the antipsychotic medicine and refer to an acute medical facility, where the following supportive treatment should be offered *(2)*.

1. Initiate supportive measures:

Ensure oxygen, correct hypotension with intravenous fluids, reduce temperature (e.g. cooling blankets, antipyretics, cooled intravenous fluids, ice packs, evaporative cooling, ice-water enema).

2. Maintain vigorous hydration and alkalinization of the urine using intravenous sodium bicarbonate to prevent renal failure.
3. Consider benzodiazepines (intramuscular lorazepam) to manage agitation, if needed. Carbamazepine and clonidine are also helpful in managing agitation.

Further treatment includes:

4. Consider bromocriptine, levodopa and amantadine to reverse the state of decreased dopamine. Bromocriptine is administered orally or via nasogastric tube, starting with 2.5 mg three times daily and increasing the dose by 2.5 mg every 24 hours.
5. Dantrolene is used to treat muscular rigidity. It can be administered intravenously, starting with an initial bolus of 1–2.5 mg per kg.

4.2.5 Monitor clozapine

Clozapine is offered to people with schizophrenia whose illness has not responded adequately to treatment despite the sequential use of adequate doses of at least two different antipsychotic drugs alongside psychological therapies *(3)*. Although clozapine is initiated by a specialist, it may also be used in a community-based model. It should only be offered where laboratory facilities for monitoring white blood cell count are available.

Treatment is started at a low dose, and the dosage is increased slowly. Adverse effects also tend to be more common and severe at the beginning of the therapy.

Day 1: 12.5 mg once a day.

Blood pressure should be monitored hourly for six hours because of the hypotensive effect of clozapine. Monitoring is not usually necessary if the first dose is given at night.

Day 2: 12.5 mg twice a day.

If the person is tolerating clozapine, the dose can be increased by 25–50 mg a day, until a dose of 300 mg a day is reached. This can usually be achieved in 2–3 weeks. Further dosage increases should be made slowly in increments of 50–100 mg each week. The dose range is approximately 250 mg per day (female non-smoker) to 550 mg per day (male smoker).

The total clozapine dose should be divided (usually twice daily) and, if sedation is a problem, the larger portion of the dose can be given at night *(2)*.

Blood monitoring is mandatory for clozapine.

Check baseline blood tests (white cell count and differential count) before starting clozapine.

Continue to check full blood count weekly for the first 18 weeks and then every two weeks for the remainder of the year. After that, blood monitoring is usually done monthly (Table 4.6) *(2)*.

In countries where the obligatory monitoring for clozapine users is not feasible, it should not be prescribed *(2)*.

Table 4.6. Additional monitoring with clozapine *(2)*

Baseline	1 month	3 months	6 months	12 months
Weight/BMI/waist	Weight/BMI/waist	Weight/BMI/waist	Weight/BMI/waist	Weight/BMI/waist
Plasma glucose and lipids	Plasma glucose and lipids		Plasma glucose and lipids	Plasma glucose and lipids
Liver function tests			Liver function tests	

4.2.6 Offer treatment for severe agitation in a psychotic episode

A psychotic episode can present with severe agitation, where the person might not be willing to accept treatment. The immediate aim should be to consult or refer to a specialist.

When dealing with a person who is agitated or aggressive, it is essential to:

- Remain calm, respectful and use a gentle tone.
- Listen attentively to understand their concerns and explore potential solutions.
- Involve carers and other staff members in communication.
- Remove the person from the situation that appears to trigger the aggression.

For prompt control of acute agitation with psychotic symptoms, consider antipsychotic medicine, e.g. haloperidol and risperidone, especially when symptoms are severe or behaviour is disturbed. If a person has already been prescribed a regular antipsychotic, then consider oral lorazepam 1–2 mg and promethazine 25–50 mg *(2)*.

If oral treatment is not feasible, consider haloperidol 2 mg orally/intramuscularly hourly, up to five doses (maximum 10 mg). Consider intramuscular lorazepam 2 mg and promethazine 50 mg. Intramuscular promethazine is also an option in benzodiazepine-tolerant individuals *(2)*.

For agitation due to ingestion of substances, such as alcohol/sedative withdrawal or stimulant intoxication, use diazepam 10–20 mg orally and repeat as needed. Lorazepam or clonazepam can also be used.

If agitation does not settle down, consult a specialist *(1)*.

In cases of extreme agitation:

- Seek help from specialist mental health staff.
- Use haloperidol 5 mg intramuscularly, repeat in 15–30 minutes if needed (maximum 15 mg).
- Consult a specialist.

After intramuscular administration of antipsychotic medicines, monitor vital signs (temperature, pulse, blood pressure and respiratory rate) every 15 minutes for one hour, and then hourly until there are no further concerns about the person's physical health status *(2)*.

If the person is asleep or unconscious, the continuous use of pulse oximetry to measure oxygen saturation is desirable. ECG and monitoring are recommended *(2)*.

For any complications, refer to Table 4.7.

Table 4.7. Monitoring after using intramuscular haloperidol *(2)*

Problem	Management
Acute dystonia	Give procyclidine 5–10 mg IM or IV
Reduced respiratory rate (< 10 breaths per minute) or oxygen saturation (< 90%)	Give oxygen, raise legs, ensure the person is not lying face down
Fall in blood pressure (< 50 mmHg diastolic)	Have the person lie flat, tilt bed towards head
Irregular or slow pulse (< 50 beats per minute)	Refer to specialist medical care immediately
Increased temperature	In view of the risk of NMS and perhaps arrhythmia, check creatine kinase urgently

4.2.7 Offer long-term treatment

After the acute episode has resolved, it is generally suggested that treatment should be continued for 7–12 months, carefully balancing effectiveness and side-effects. Without treatment, two thirds of people living with psychosis relapse within one year. During long-term treatment, maintain or moderately decrease the dose administered during the acute phase, according to clinical status and circumstances.

Treatment adherence may be a major problem in the long term. In these cases:

- Consider non-pharmacological interventions to increase adherence (psychoeducation for the person and family, specific psychotherapeutic interventions).
- Discuss with the person and/or carers switching to a long-acting injection antipsychotic medicine. These include fluphenazine, haloperidol, paliperidone, risperidone and zuclopenthixol.

In persons with psychotic symptoms persisting more than three months, the medicine may be continued for several years even after the symptoms resolve.

When considering stopping the medicine, the risks of relapse should be weighed against long-term medication side-effects and discussed with the person and their family. If possible, consult a specialist.

To stop the medicine:

- Gradually reduce the dose.
- Educate individuals and family members to recognize early symptoms of relapse.
- Follow up regularly.

4.2.8 Overdosage of antipsychotic medicines *(2)*

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

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

If overdosage of antipsychotics is suspected, refer to an acute medical facility.

4.2.9 Special populations

Older adults

- Do not prescribe antipsychotics in people with dementia *(2)*.
- In older adults with cognitive impairment or dementia who present with behavioural symptoms, use antipsychotics with caution.
- Avoid fluphenazine as there is an increased risk of parkinsonian and anticholinergic side-effects *(2)*.
- Monitor risk of drug interactions carefully if the person is on other medicines.
- Antipsychotics carry an increased risk of cerebrovascular events and death in older adults with dementia-related psychosis.

Women who are pregnant or breastfeeding

- Consider consultation with a mental health specialist, if available.
- Explain the risk of adverse consequences for the mother and her baby, including obstetric complications and psychotic relapses, particularly if the medicine is stopped.

- Consider low-dose oral haloperidol or chlorpromazine for women with psychosis who are planning a pregnancy or are pregnant or breastfeeding. Olanzapine can be used in women who are pregnant and breastfeeding *(2)*.
- Do not prescribe anticholinergics to women who are pregnant due to the extrapyramidal side-effects of antipsychotic medicines, except in cases of acute short-term use.
- Do not prescribe depot antipsychotics routinely to women who are planning a pregnancy, pregnant or breastfeeding, because of safety concerns.

Children and adolescents

- Consult with a mental health specialist. Do not prescribe antipsychotics in children *(2)*.
- In adolescents with psychotic disorders, oral antipsychotic medicines (aripiprazole, olanzapine, paliperidone, quetiapine, risperidone) should be considered under specialist supervision after carefully balancing effectiveness, side-effects, and person and carer preference.
- In adolescents with a treatment-resistant psychotic disorder, clozapine should be considered under specialist supervision after carefully balancing effectiveness, side-effects, and person and carer preference. It should only be offered where laboratory facilities for monitoring white blood cell count are available.
- First-generation antipsychotics should be avoided in children and adolescents. Children and adolescents are at greater risk than adults for side-effects *(2)*.

4.3 Bipolar disorder

This section is focused on mood stabilizer agents. These are prescribed either to treat a manic episode or to prevent recurrent episodes in people with bipolar affective disorder.

- For treatment of depressive episodes, fluoxetine, olanzapine, quetiapine, valproic acid (sodium valproate) or venlafaxine should be considered. Regular monitoring is advised because antidepressants alone can lead to mania in people with bipolar depression *(1)*.
- If fluoxetine or venlafaxine are chosen, they should be combined with a mood stabilizer (quetiapine, olanzapine, carbamazepine, valproic acid (sodium valproate) or lithium) (Table 4.8) *(1)*.

4.3.1 Treat a manic episode

For prompt control of acute manic episodes with psychotic symptoms, consider oral antipsychotic medicines (aripiprazole, haloperidol, olanzapine, paliperidone or quetiapine) or mood stabilizers (carbamazepine, lithium, valproic acid (sodium valproate) *(2)*.

Valproic acid (sodium valproate) should not be used in women and girls of childbearing potential owing to the high risk of birth defects and developmental disorders in children in utero.

If response is inadequate, then antipsychotic medicines and sodium valproate or lithium may be used in combination (only under specialist care).

For behavioural disturbances or agitation in a manic episode, consider benzodiazepines for a short term *(1)*. In view of the risk of dependence, benzodiazepine for the treatment of anxiety disorder in primary care should be prescribed as a short-term measure (3–7 days maximum) ONLY during crises *(2)*.

A manic episode can present with severe agitation where the person might not be willing to accept treatment. These cases should be immediately discussed with or referred to a specialist.

If there is risk of harm to self or others, refer to a specialist.

If oral treatment is not feasible, see section 4.2.6.

4.3.2 Offer long-term treatment (to prevent recurrent episodes)

Long-term pharmacological interventions to prevent relapse, particularly treatment with lithium, should be planned under the supervision of a specialist, and after taking into account medicine that has been effective during previous episodes of mania. At least six months on medicine is needed to determine the full effectiveness of maintenance treatment *(1)*.

Lithium is the most effective long-term treatment for bipolar disorder, but discuss with the person whether they prefer to continue the previous treatment or switch to lithium.

Lithium has a narrow therapeutic index, and blood levels must be monitored. Severe toxic effects can occur when renal excretion is impaired *(2)*.

Please note that lithium is not suitable if:

- Clinical or laboratory monitoring for lithium is not available *(1)*.
- Lithium is not considered safe e.g. in renal disease *(2)*.
- No specialist is available to supervise lithium prescription (1).

If lithium is not suitable, consider sodium valproate and carbamazepine. Discuss with the person the possible benefits and risks for them of each drug *(1)*.

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

Do not offer sodium valproate to women of childbearing potential *(5)*.

4.3.3 Start lithium

Before starting lithium therapy, it is mandatory to check:

- The person's weight or BMI.
- Full blood count.
- Renal function tests.
- Thyroid function tests.
- ECG.
- Pregnancy test (if indicated).

If these laboratory examinations are not feasible, lithium should not be prescribed.

Always discuss:

- That poor adherence or rapid discontinuation may increase the risk of relapse.
- Women of childbearing age should use a reliable form of contraception.
- Ensure that the person maintains their fluid intake, particularly after sweating (e.g. after exercise, in hot climates or if they have a fever).
- The importance of not taking over-the-counter non-steroidal anti-inflammatory drugs.
- Interactions with other drugs: angiotensin-converting enzyme inhibitors, thiazide diuretics, metronidazole and tetracycline are known to potentially elevate lithium levels.

Seek medical attention if the person develops diarrhoea or vomiting or becomes acutely ill for any reason *(2)*.

Monitoring of plasma levels:

- Measure plasma lithium levels one week after starting lithium and one week after every dose change, and weekly until levels are stable.
- Blood should be taken 12 hours after the last dose *(2)*.

Monitor every 2–3 months (Table 4.9).

Table 4.8. Mood stabilizers *(1)*

Medicine	Dosage	Maximum dose
Lithium	Start 400 mg/day orally (for older adults 200 mg per day) Increase gradually every seven days until target blood level reached	600–1200 mg per day
Sodium valproate	Start 500 mg per day orally Increase slowly to 1000–2000 mg/day	60 mg per kg per day
Carbamazepine	Start 200 mg per day orally Increase by 200 mg weekly to 400–600 mg daily in two divided doses	1200 mg per day

Table 4.9. Target plasma levels for lithium *(2)*

Target group	Target plasma lithium level
Acute treatment of mania	0.8–1.0 mmol per litre
Maintenance treatment of bipolar disorder	
Standard lithium serum levels	0.6–0.8 mmol per litre
People with good response but poor tolerance	0.4–0.6 mmol per litre
People with insufficient response and good tolerance	0.8–1.0 mmol per litre

Check plasma lithium levels every three months for the first year.

After the first year, measure plasma lithium levels every six months, or every three months for people in any of the following groups *(5)*:

- Older people.
- People taking drugs that interact with lithium.
- People who are at risk of impaired renal or thyroid function, raised calcium levels or other complications.
- People with impaired thyroid function.
- People who have poor symptom control.
- People with poor adherence.

Once the person is stable on lithium, every six months check *(5)*:

- The person's weight or BMI.
- Full blood count.
- Renal function tests (including calcium levels).
- Thyroid function tests.
- ECG.

Monitor the person at every appointment for symptoms of neurotoxicity, including paraesthesia, ataxia, tremor and cognitive impairment, which can occur even at therapeutic levels of lithium (Table 4.10) *(5)*.

Table 4.10. Side-effects of mood stabilizers *(1)*

Medicine	Common side-effects	Serious side-effects	Contraindications/ cautions *(see section 4.3.8 for special populations)*
Lithium	Sedation, cognitive problems, tremor, impaired coordination, hypotension, leukocytosis, polyuria, polydipsia, nausea, diarrhoea, weight gain, hair loss, rash	Diabetes insipidus, hypothyroidism, ECG changes (arrhythmia, sick sinus syndrome, T-wave changes) Lithium toxicity can cause seizures, delirium, coma, death	Do NOT prescribe for persons with severe cardiac or renal disease
Valproic acid (sodium valproate)	Sedation, headache, tremor, ataxia, nausea, vomiting, diarrhoea, weight gain, transient hair loss	Impaired hepatic function, thrombocytopenia, leukopenia, drowsiness/confusion, liver failure, haemorrhagic pancreatitis	Caution in persons with underlying or suspected hepatic disease Monitor liver function tests and platelets if possible
Carbamazepine	Sedation, confusion, dizziness, ataxia, double vision, nausea, diarrhoea, benign leukopenia	Hepatotoxicity, cardiac conduction delay, low sodium levels, severe rash	Do NOT prescribe for persons with blood disorders, kidney, liver or cardiac disease

4.3.4 Start sodium valproate or carbamazepine *(5)*

Before starting sodium valproate, check:

- Medical history of cardiovascular, renal or hepatic conditions.
- The person's weight or BMI.
- Full blood count.
- Renal function tests.
- Liver function tests.
- Pregnancy test, if applicable.

Monitor sodium valproate or carbamazepine:

- Measure the person's weight or BMI and carry out liver function tests and a full blood count again after six months of treatment with sodium valproate, and repeat annually.
- Monitor sedation, tremor and gait disturbance carefully in older people.

4.3.5 Follow-up

Initial follow-up should be as frequent as possible, even daily, until acute symptoms respond to treatment.

Regular follow-up is needed. Once symptoms respond, monthly to quarterly follow-up is recommended (based on clinical need and feasibility factors such as staff availability, distance from clinic, etc.) *(1)*.

If no improvement is seen after 4–6 weeks of treating a manic episode, refer to a specialist to explore the possibility of augmenting the treatment in combination strategies (antipsychotic plus lithium or antipsychotic plus sodium valproate) *(1)*.

If adverse reactions are troubling, decrease the dose. If adverse reactions persist despite a reduction in dose, consider switching to another antimanic agent *(1)*.

Sleep disturbances can trigger or exacerbate mood episodes, including manic and depressive episodes. Stabilizing sleep patterns can be an effective strategy for preventing relapse in bipolar disorder. This involves developing a regular sleep schedule, establishing a relaxing bedtime routine and avoiding caffeine and other stimulants close to bedtime *(4)*.

4.3.6 When and how to stop treatment

Maintenance therapy with mood stabilizers or antipsychotic medicines should be continued for at least six months after the person completely recovers.

Before stopping medicine, discuss with the person how to recognize early signs of relapse and what to do if symptoms recur. Reduce gradually over a period of weeks or months.

Do not stop lithium abruptly unless there is a serious adverse effect. Withdraw gradually over at least a month and preferably longer if practicable *(2)*.

Offer regular follow-up after stopping medicine.

4.3.7 Overdosage of mood stabilizers

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

The severity of chronic lithium intoxication correlates directly with the serum lithium concentration and may be categorized

as mild (1.5–2.0 mEq per litre), moderate (2.0–2.5 mEq per litre) or severe (> 2.5 mEq per litre) *(5)*.

Several factors might lead to impairment in lithium secretion. Sodium and volume depletion due to any conditions such as vomiting, diarrhoea, febrile illness, renal insufficiency, excessive exercise, water restriction, excessive sweating, low sodium diet and congestive heart failure may increase the risk of lithium toxicity *(7)*.

Symptoms associated with mild toxicity include lethargy, drowsiness, coarse tremor, muscle weakness, nausea, vomiting and diarrhoea. Moderate toxicity is associated with confusion, dysarthria, nystagmus, ataxia, myoclonic twitches and ECG changes. Severe toxicity is associated with grossly impaired consciousness, increased deep tendon reflexes, seizures, syncope, renal insufficiency, coma and death *(6)*.

The symptoms of carbamazepine overdose include somnolence, tachycardia, atrioventricular conduction defects, seizures, coma, nystagmus, hyporeflexia or hyperreflexia, rigidity, orofacial dyskinesia and mild respiratory depression *(2)*.

The symptoms of valproic acid overdose include hypotension, somnolence, convulsions, coma, respiratory depression and blood dyscrasia *(2)*.

4.3.8 Special populations

Older adults

Prescribe lower doses.

Pregnant women

Consult a specialist when available.

Do NOT prescribe lithium, sodium valproate or carbamazepine 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.

Carbamazepine has known teratogenic effects *(2)*.

If sodium valproate is taken during pregnancy, up to four in 10 babies are at risk of developmental disorders, and approximately one in 10 is at risk of birth defects *(5)*.

Weigh the risks and benefits of medicines in women of childbearing age.

If a pregnant woman develops acute mania while taking mood stabilizers, consider switching to a low dose of haloperidol (olanzapine and quetiapine are also options), in consultation with a specialist if available *(3)*.

Breastfeeding women

Lithium is contraindicated in breastfeeding. Lithium and haloperidol are excreted in breast milk. However, the amount of carbamazepine or sodium valproate excreted is extremely low and these medicines can be used during breastfeeding.

Renal or hepatic impairment *(2)*

Lithium is contraindicated in severe renal impairment, as the risk of toxicity is increased.

Carbamazepine and sodium valproate do not generally require dose adjustment in renal impairment.

Carbamazepine and sodium valproate are contraindicated in acute liver disease.

In chronic liver disease, consider lower doses.

Lithium does not generally require dose adjustment in liver impairment. Consider switching to lithium when possible.

Persons living with HIV/AIDS *(5)*

Sodium valproate is the preferred choice in men living with HIV/AIDS, due to drug–drug interactions. However, it is not appropriate in females living with HIV/AIDS.

Adolescents

Psychotropic medicines (antipsychotic medicines, namely aripiprazole, olanzapine, quetiapine and risperidone, and mood stabilizers, namely lithium) should be considered under specialist supervision for adolescents with bipolar disorder.

References

1. mhGAP intervention guide for mental, neurological and substance use disorders in non-specialized health settings: mental health Gap Action Programme (mhGAP) – version 2.0. Geneva: World Health Organization; 2016 (https://www.who.int/publications/i/item/9789241549790).

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MODULE 5
DEMENTIA

Currently, no treatment exists to cure dementia. Therapeutic interventions are therefore targeted at specific symptoms or at improving or slowing the decline in cognitive function.

Pharmacological treatment of dementia should always be integrated with psychosocial interventions as part of a comprehensive management plan, and not offered in isolation. Medicines alone should only be considered when psychological interventions are either not available or people prefer pharmacological treatment only.

Refer to the mhGAP-IG for an overview of assessment and management, including psychosocial interventions.

5.1 Educate the person/carers

Explain:

- Dementia is an illness of the brain and not part of ageing, and tends to get worse over time.
- Although there is no cure, there is much that can be done to help and support the person and their family.
- Many specific concerns and behaviours can be managed as they arise.
- A lot can be done to make the person more comfortable and to make providing support less stressful for carers.

5.2 Dementia with behavioural and/or psychological symptoms

- Provide psychosocial interventions first.
- Haloperidol and atypical antipsychotics should not be used as first-line management for behavioural or psychological symptoms of dementia.
- If there is clear and imminent risk of harm with severe and distressing symptoms, the short-term use of haloperidol or atypical antipsychotic medicines may be considered, preferably with a specialist.
- Follow the principle of: "start low, go slow" (titrate) and review needs regularly (at least monthly).
- Use the lowest effective dose.
- Monitor the person for EPS.
- Avoid intravenous haloperidol.
- Avoid diazepam *(1).*

5.3 Dementia without behavioural and/or psychological symptoms

Do NOT routinely prescribe cholinesterase inhibitors for any type of dementia.

Consider medicines only when:

- A specific diagnosis of Alzheimer's disease has been made.
- Support and supervision by specialists are available.
- Carers can carefully monitor side-effects and response *(1).*

5.4 Select medicine

The drugs used in dementia are acetylcholinesterase inhibitors (AChE-I) (donepezil, galantamine and rivastigmine) or glutamate receptor antagonists (memantine) (Table 5.1). Please consult a specialist if available.

Select a drug after considering availability, cost, adverse effects profile, expectations about adherence, medical comorbidity, possibility of drug interactions and dosing profiles.

- For mild to moderate Alzheimer's disease, consider donepezil, galantamine and rivastigmine.
- For dementia with associated vascular disease, consider memantine.
- For mild to moderate dementia with Parkinson's disease, consider rivastigmine *(3).*
- For people with Alzheimer's disease who are intolerant of, or have a contraindication to, cholinesterase inhibitors, memantine can be prescribed in a specialist setting.
- For severe Alzheimer's disease, memantine can be prescribed in a specialist setting *(3).*

Therapy with AChE-I should be initiated with a drug with the lowest acquisition cost (taking into account the required daily dose and the price per dose once shared care has started).

An alternative may be considered on the basis of adverse effects profile, expectations about adherence, medical comorbidity, possibility of drug interactions and dosing profiles *(1).*

Table 5.1. Dosage of different drugs used in dementia *(2)*

Medicine	Starting dose	Usual treatment dose	Recommended interval between dose increase
Donepezil	5 mg daily	10 mg daily	Increase by 5 mg after four weeks
Rivastigmine	1.5 mg twice a day orally 4.6 mg daily for patch	6–12 mg twice a day orally 9.5 mg/24-hour patch Consider 13.3 mg/24-hour patch: – If 9.5 mg regimen is tolerated and meaningful cognitive decline occurs – For severe dementia	Orally: Increase by 1.5 mg after two weeks Patch: Increase dose after a minimum of four weeks from previous dose *(3)*
Galantamine	8 mg XL (prolonged release) daily	16–24 mg XL daily	Increase by 8 mg XL after four weeks
Memantine	5 mg daily	20 mg daily (or 10 mg twice a day)	Increase by 5 mg weekly after one week

5.5 Monitor treatment

Offer regular follow-up to monitor for side-effects and any changes in cognitive function (Table 5.2). Involve the family to monitor side-effects closely at home.

Table 5.2. Side-effects of medicines used in dementia *(2)*

Medicine	Common side-effects	Caution
Donepezil	Diarrhoea, nausea, headache, common cold, anorexia, hallucinations, agitation, aggressive behaviour, abnormal dreams and nightmares, syncope, dizziness, insomnia, vomiting, abdominal disturbance, rash, pruritus, muscle cramps, urinary incontinence, fatigue, pain	Caution in persons with cardiovascular disease
Rivastigmine	Nausea, vomiting, decreased appetite, hallucinations, depression, syncope, dizziness, tremor, headache, somnolence, lethargy, bradycardia, hypertension, abdominal pain and discomfort, diarrhoea, dyspepsia, muscle spasms, fatigue, asthenia, malaise, weight loss, fall	Caution in persons with cardiovascular disease
Galantamine	Nausea, vomiting, decreased appetite, hallucinations, depression, syncope, dizziness, tremor, headache, somnolence, lethargy, bradycardia, hypertension, abdominal pain and discomfort, diarrhoea, dyspepsia, muscle spasms, fatigue, asthenia, malaise, weight loss, fall	Caution in persons with cardiovascular disease
Memantine	Drug hypersensitivity, somnolence, dizziness, balance disorders, hypertension, dyspnoea, constipation, elevated liver function test, headache	Caution in individuals with dementia who have a history of bradycardia or epilepsy

5.6 When and how to stop treatment

The medicine needs to be discontinued if:

- The person/caregiver decides to discontinue (after being advised on the risks and benefits of stopping treatment).
- There are problems with compliance which cannot be reasonably resolved.
- The person's cognitive, functional or behavioural decline is worsened by treatment.
- There are intolerable side-effects.
- Comorbidities make treatment risky.
- There is no clinically meaningful benefit to continuing therapy.

When a decision is made to stop treatment (for reasons other than lack of tolerability), taper the dose and monitor for evidence of significant decline during the next 1–3 months.

If such a decline occurs, consider reinstatement of treatment *(2)*.

References

1. mhGAP intervention guide for mental, neurological and substance use disorders in non-specialized health settings: mental health Gap Action Programme (mhGAP) – version 2.0. Geneva: World Health Organization; 2016 (https://www.who.int/publications/i/item/9789241549790).

2. Taylor DM, Barnes TRE, Young AH. The Maudsley Prescribing Guidelines in psychiatry, 14th edition. John Wiley & Sons; 2021.

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MODULE 6
SUBSTANCE USE DISORDERS

This module includes:

- Nicotine dependence.
- Alcohol dependence.
- Opioid dependence.

Pharmacological treatment of substance use disorders should always be offered in combination with psychosocial interventions as part of a comprehensive management plan. Pharmacological interventions alone should only be considered when psychological interventions are either not available or people prefer pharmacological treatment only *(1)*.

Refer to mhGAP-IG for an overview of assessment and management, including psychosocial interventions.

6.1 Nicotine dependence

In addition to behavioural therapies, there are pharmacological therapies available to help overcome nicotine withdrawal symptoms. There are two major types of medication available that may be able to relieve withdrawal symptoms:

1. Nicotine replacement therapies (NRTs).
2. Non-nicotine-based therapies *(2)*.

NRTs include aids such as nicotine gum and patches while non-nicotine therapies include medications such as bupropion and varenicline (Table 6.1) *(2)*.

All of these treatments at least double the chances of a person successfully stopping smoking *(3)*.

Table 6.1. NRTs, bupropion and varenicline *(2)*

Medication	How to use	Side-effects
Nicotine gum (over the counter): delivers nicotine through the lining of the mouth (available as 2 mg and 4 mg)	Dose: Based on number of cigarettes per day (CPD) > 20 CPD: 4 mg < 20 CPD: 2 mg Based on time to first cigarette of the day < 30 min: 4 mg > 30 min: 2 mg Initial dosage is 1–2 pieces every 1–2 hours (10–12 pieces a day). Taper as tolerable Duration of use: up to 12 weeks with no more than 24 pieces used per day How to use: it is not chewed like regular gum but is chewed briefly until a "peppery" taste is noticed. Then it is placed between cheek and gum for about 30 minutes	Hiccups, jaw ache, stomach irritation, sore mouth
Nicotine patch (over the counter): delivers nicotine through skin (available as 24-hour delivery in 7 mg, 14 mg and 21 mg, and as 16-hour delivery in 5 mg, 10 mg and 15 mg)	Dose: (24-hour patch) > 40 CPD: 42 mg per day 21–39 CPD: 28–35 mg per day 10–20 CPD: 14–21 mg per day < 10 CPD: 14 mg per day Adjust based on withdrawal symptoms, urges and comfort. After four weeks of abstinence, taper every two weeks in 7–14 mg steps as tolerated Duration: 8–12 weeks How to use: patches may be placed on any hairless area on the upper body including arms and back. Rotate the patch site each time a new patch is applied to lessen skin irritation	Skin irritation, allergy (not suitable if person has chronic conditions), vivid dreams and sleep disturbances

Bupropion (prescription): originally used as an antidepressant; affects the levels of neurotransmitters, affecting the urge to smoke (available in 150 mg sustained-release tablets)	Dose: take doses at least eight hours apart, start medication one week prior to the target quit date (TQD). 150 mg once daily for three days, then 150 mg twice daily for four days, then on TQD stop smoking. Continue at 150 mg twice daily for 12 weeks. Medication may be stopped abruptly, no need to taper	Insomnia, dry mouth, nervousness/difficulty concentrating, rash, headache, dizziness, seizures (risk is 1 in 1000) Warnings: people should stop bupropion and contact their doctor if they experience agitation, depressed moods, and/or any changes in behaviour that are not typical of nicotine withdrawal or if they experience suicidal thoughts or behaviours
Varenicline (prescription): attaches to nicotine receptors, partially blocking the reward effects of nicotine and partially stimulating the nicotine receptors (available in 0.5 mg and 1 mg)	Dose: take with food, start medication one week prior to the TQD. 0.5 mg once daily for three days, then 0.5 mg twice daily for four days, then on TQD stop smoking and take 1 mg twice daily for 11 weeks. May be stopped abruptly, no need to taper	Nausea, sleep disturbances (insomnia, abnormal dreams), constipation, flatulence, vomiting Warnings: same as for bupropion

6.2 Alcohol dependence

For a complete overview of assessment and psychosocial interventions for drug and alcohol use disorders (including acute intoxication, overdose and withdrawal), refer to the mhGAP guides (mhGAP-IG and mhGAP-HIG).

The following challenges can present with alcohol dependence in primary care:

- Alcohol intoxication.
- Alcohol withdrawal.
- Relapse in alcohol dependence.
- Wernicke's encephalopathy..

6.2.1 Manage alcohol intoxication *(1)*

The following signs may indicate alcohol intoxication:

- Smell of alcohol on the breath.
- Slurred speech.
- Uninhibited behaviour.
- Disturbance in the level of consciousness, cognition, perception, affect or behaviour.
- Suspect sedative intoxication/overdose in anyone with unexplained drowsiness and slow breathing.
- Normal pupils (if these are pinpoint, suspect opioid intoxication).

To manage alcohol intoxication, offer supportive care and observe the person until fully recovered:

- Check airway, breathing and circulation.
- Provide initial respiratory support:
  - Protect airway and breathing as respiratory depression due to alcohol intoxication may result in death.
  - Lay the person on their side to prevent aspiration.
  - Give oxygen, if available.
- Rehydrate but do not give fluids orally if the person is sedated (alcohol is a diuretic).
- If there are signs of dehydration (dry lips and mucosae, poor urine output), consider intravenous fluids.
- Check glucose (many individuals with alcohol use disorder may have hypoglycaemia), and correct hypoglycaemia with 5% dextrose intravenously.

If the person is minimally responsive, unresponsive or in respiratory failure:

- Provide supportive care.
- Monitor vital signs.
- Lay the person on their side to prevent aspiration.
- Give oxygen if available.
- Consider intravenous rehydration but do not give fluids orally while sedated.
- Observe the person until fully recovered or transported to hospital.

6.2.2 Manage alcohol withdrawal

Withdrawal is the experience of a set of unpleasant symptoms following an abrupt cessation or reduction in dose of a psychoactive substance. The substance will have been consumed in high enough doses and for a long enough duration for the person to be physically or mentally dependent on it. Withdrawal symptoms are, essentially, opposite to those that are produced by the psychoactive substance itself. In the case of alcohol these may include: tremors, shaking, nausea/vomiting, increased heart rate and blood pressure, seizures, agitation, confusion and hallucinations. Such symptoms can be life-threatening *(1)*.

Sudden alcohol cessation can lead to seizures, delirium and even death. If an individual is willing to stop using alcohol, support must be provided. Determine the appropriate setting to cease alcohol use, and arrange inpatient withdrawal management, if necessary *(1)*.

Outpatient withdrawal management is usually possible when:

- There is a supervising carer, ideally for 24 hours a day, throughout the duration of the withdrawal management process.
- The treatment plan has been agreed with the person, their carer and their primary care physician/GP.
- A contingency plan has been agreed with the person, their carer and their primary care physician/GP.
- Outpatient programmes including psychosocial support are available *(3)*.

Outpatient withdrawal management is challenging (can involve complications) when:

- There is a history of seizures or delirium tremens.
- The person is very young or old.
- There is current use of other drugs in addition to alcohol, especially sedatives (benzodiazepines, opioids, barbiturates).
- There is a comorbid mental or physical health condition, learning disability or cognitive impairment.
- The person is pregnant.
- The person is homeless or has no social support.
- There is a history of unsuccessful withdrawal management *(3)*.

Diazepam for withdrawal symptoms

Outpatient setting

In the case of planned withdrawal management, alleviate symptoms using diazepam (Table 6.2). The dose and duration of diazepam treatment varies according to the severity of the withdrawal. Administer diazepam orally at an initial dose of up to 40 mg daily (10 mg four times a day or 20 mg twice a day) for 3–7 days. Gradually decrease the dose and/or frequency as soon as symptoms improve. Monitor the person frequently, as each person may respond differently to this medicine *(1)*.

Hospital setting

In a hospital setting, diazepam can be given more frequently, (i.e. hourly) and at higher daily doses, up to (orally) 120 mg daily for the first three days, if necessary and based on frequent assessment of the person's withdrawal symptoms and mental status (Table 6.2) *(1)*.

Somatic complaints are common during assisted withdrawal from alcohol. Table 6.3 shows the recommended treatments for these symptoms.

Table 6.2. Diazepam for treating withdrawal symptoms

Dose	Side-effects	Caution
In an outpatient setting: 5–10 mg up to four times a day In an inpatient setting: 10–20 mg every two hours until features of alcohol withdrawal/stimulant intoxication are no longer observable or the person is lightly sedated Maximum dose up to 120 mg daily for the first three days	Sedation and respiratory depression, which can be life-threatening Prolonged use can lead to tolerance, withdrawal and dependence on benzodiazepines	Use caution when initiating or increasing the dose of benzodiazepines, as they can cause respiratory depression. Use caution in persons with respiratory disease and/or hepatic encephalopathy Do not use in people who are sedated Individuals should not drive or operate machinery Caution in use: - With other sedatives - In persons with respiratory disease - In persons with liver disease Alternatively, a shorter-acting benzodiazepine such as oxazepam may be used Supervise dosing to minimize the risk of diversion (i.e. selling the medicine to somebody else)

Table 6.3. Treatment of somatic symptoms *(3)*

Symptom	Management
Dehydration	Ensure adequate fluid intake in order to maintain hydration and electrolyte balance. Dehydration can precipitate life-threatening cardiac arrhythmia
Pain	Paracetamol (acetaminophen)
Nausea and vomiting	Metoclopramide 10 mg or prochlorperazine 5 mg, 4–6 hourly
Diarrhoea	Diphenoxylate and atropine (Lomotil) or loperamide
Skin itching	Occurs commonly and not only in individuals with alcoholic liver disease: use oral antihistamines

6.2.3 Prevent relapse in alcohol dependence

Consider medicines including acamprosate, naltrexone and disulfiram to prevent relapse in alcohol dependence (Table 6.4). With these medicines, an effective response may include a reduction in the quantity and frequency of alcohol consumption, if not complete abstinence *(1)*.

In a specialist setting, baclofen can also be used (*note*: baclofen is associated with risk of abuse). It can be useful particularly among individuals who are non-responsive or with counterindications against first-line medications (acamprosate, disulfiram and naltrexone) for the treatment of alcohol dependence *(3)*.

Table 6.4. Medicines used to prevent relapse in alcohol dependence

Medicine	Dose	Side-effects	Cautions
Acamprosate (333 mg) *(1)*	Two tablets orally three times per day for 12 months If the person weighs less than 60 kg: two tablets orally two times per day for 12 months	Diarrhoea, flatulence, nausea/vomiting, abdominal pain, depression, anxiety, suicidality, itching Occasionally: maculopapular rash Rarely: bullous skin reactions	In moderate kidney disease, give one tablet orally three times per day Contraindicated in severe kidney disease and liver disease
Disulfiram *(1)*	200–400 mg daily	Drowsiness, dizziness, headache, flushing, sweating, dry mouth, nausea, vomiting, tremor, foul body odour, sexual dysfunction Rarely: psychotic reactions, allergic dermatitis, peripheral neuritis, hepatic cell damage Severe reactions can lead to: confusion, cardiovascular collapse, death	Sensitization to alcohol continues for 6–14 days after taking disulfiram, even in small amounts. DO NOT use: - With alcohol, as reactions can be life-threatening - In women who are pregnant or breastfeeding - In persons with hypertension - In persons with heart disease - In persons with liver disease - In persons with kidney disease - In persons with a history of cerebrovascular accidents - In persons with psychosis - In persons with impulsivity - In persons at risk of suicide TCAs, monamine oxidase inhibitors, antipsychotics, vasodilators and alpha or beta adrenergic antagonists make the disulfiram–alcohol reaction more serious
Naltrexone *(1)*	50 mg daily for 6–12 months In opioid dependence, ensure that there has been no opioid use in the last seven days (e.g. by administration of dose of naloxone)	Sedation, dizziness, nausea/vomiting, abdominal pain, insomnia, anxiety, reduced energy, joint and muscle pain	Monitor liver function due to risk of liver toxicity Risk of FATAL OVERDOSE in individuals who use opioids more than 24 hours after their last dose of naltrexone, due to the rapid loss of antagonistic effect DO NOT use in persons with liver failure or acute hepatitis
Baclofen *(3)*	10 mg three times a day initially Can be increased, based on safety, tolerability and an individual's response	Sedation, depression, vertigo, somnolence, numbness and muscle rigidity	Baclofen should be reduced gradually rather than stopped abruptly because of the risk of a mild benzodiazepine-like withdrawal syndrome

6.2.4 Wernicke's encephalopathy

Chronic heavy users of alcohol are at risk for Wernicke's encephalopathy, a thiamine deficiency syndrome characterized by confusion, nystagmus, ophthalmoplegia (trouble with eye movements) and ataxia (uncoordinated movements).

The "classical" triad of ophthalmoplegia, ataxia and confusion is rarely present in Wernicke's encephalopathy, and the syndrome is much more common than is recognized *(3)*. A presumptive diagnosis of Wernicke's encephalopathy should therefore be made in any person undergoing detoxification who experiences any of the following signs:

- Ataxia.
- Hypothermia.
- Hypotension.
- Confusion.
- Ophthalmoplegia/nystagmus.
- Memory disturbance.
- Unconsciousness/coma.

Any history of malnutrition, recent weight loss, vomiting or diarrhoea or peripheral neuropathy should also be noted *(3)*.

Prophylactic thiamine:

Prescribe oral thiamine for the prevention of Wernicke-Korsakoff syndrome where any of the following apply:

- Malnourishment or at risk of malnourishment.
- Decompensated liver disease.
- Acute withdrawal.
- Before and during a planned medically assisted alcohol withdrawal *(3)*.

The recommended dose is 200–300mg daily in divided doses.

Thiamine should be continued for as long as malnutrition is present and/or during periods of alcohol consumption *(1)*.

Following successful alcohol withdrawal, thiamine should be continued for six weeks. If after this time the person remains abstinent and has regained adequate nutritional status, thiamine should be discontinued. Thiamine should be restarted if the person starts drinking again *(3)*.

Glucose is administered intravenously in severely malnourished individuals.

Table 6.5. Thiamine dosage *(1)*

Medicine	Dose	Cautions
Thiamine (vitamin B1)	100 mg per day orally daily for five days to prevent Wernicke's encephalopathy 100–500 mg IV or IM 2–3 times daily for 3–5 days to treat Wernicke's encephalopathy	As thiamine is required to utilize glucose, a glucose load in a thiamine-deficient person can precipitate Wernicke's encephalopathy Parenteral B-complex must be administered before glucose is administered in all individuals presenting with altered mental status *(3)*

6.2.5 Special populations

Pregnant or breastfeeding women

- Health care providers should ask all pregnant women about their use of alcohol as early as possible in the pregnancy and at every antenatal visit *(4)*.
- Pregnant women who develop withdrawal symptoms following the cessation of alcohol consumption should be offered inpatient care with the short-term use of a long-acting benzodiazepine *(4)*.
- Breastfeeding women using alcohol should be advised and supported to cease alcohol use. However, alcohol use is not necessarily a contraindication to breastfeeding *(4)*.

6.3 Opioid dependence

For a complete overview of assessment and psychosocial interventions for drug and alcohol use disorders (including acute intoxication, overdose and withdrawal), refer to the mhGAP guides (mhGAP-IG and mhGAP-HIG).

The following management challenges can present with opioid use in primary care:

1. Manage opioid intoxication and overdose.
2. Manage opioid withdrawal.
3. Manage opioid dependence.
4. Prevent relapse in opioid dependence.

6.3.1 Manage opioid intoxication and overdose

Opioid overdose is a preventable cause of death in the opioid-using population. This includes overdose on illicit opioids such as heroin and overdose on prescribed opioids such as methadone or buprenorphine.

If any person using opioids presents with a low level of consciousness and depressed respiratory function, opioid overdose must be suspected *(5)*.

Opioid overdose is clinically characterized by:

- Unconsciousness.
- A low respiratory rate (12 breaths per minute).
- Pinpoint pupils.
- Cyanosis.
- Cold, clammy skin *(5)*.

Offer basic life support:

Apply vigorous stimulation, check and clear airway, check respiration, look for chest rising and falling *(5)*.

In the presence of vomit, seizures or irregular breathing, turn the person on their side and, if necessary, clear the airway of vomit.

In the absence of regular breathing, provide rescue ventilation and administer naloxone *(5)*.

If there are no signs of life, commence chest compressions. Readminister naloxone after 2–3 minutes if necessary *(5)*.

Administer naloxone:

Naloxone is an opioid receptor antagonist that can reverse opioid overdose (Table 6.6). It can be administered by a variety of routes including intravenously, intramuscularly, subcutaneously and intranasally *(5)*.

The route of administration is selected based on the formulation available, the skill of the health professional and the setting.

The initial dose should be 0.4–2 mg, targeting recovery of breathing *(5)*.

Readminister naloxone after 2–3 minutes if necessary.

In most cases, 0.4–0.8 mg is an effective dose.

Observe for 1–2 hours and repeat naloxone as needed *(5)*.

Continue to resuscitate and observe until breathing resumes or the person is transported to a hospital *(1)*.

In all cases call for professional assistance. It is essential that expert professional assistance be sought as soon as possible. Even in the case of opioid overdose, a person may not respond to naloxone if other drugs have been taken.

Table 6.6. Medicine to treat opioid overdose *(1)*

Medicine	Dose	Side-effects
Naloxone	0.4–2 mg IV, IM or subcutaneous Intranasal delivery may require a higher dose It should be noted that the commonly used method of intranasal administration is to spray 1 ml of the 1 mg per ml formulation of naloxone into each nostril with an atomizer connected to a syringe Repeat doses as needed	Discomfort or withdrawal symptoms may result

6.3.2 Manage opioid withdrawal

Withdrawal management aims to assist people dependent on opioids to withdraw from them completely. Pharmacological management of opioid withdrawal is usually by one of the following:

- Gradual cessation of an opioid agonist (e.G. Methadone).
- Short-term use of a partial agonist (e.G. Buprenorphine).
- Sudden opioid cessation and use of alpha-2 adrenergic agonists to relieve withdrawal symptoms.

In practice, most persons resume opioid use within six months of commencing opioid withdrawal; the implication being that a single detoxification episode should not be promoted as effective treatment.

Before embarking upon withdrawal from opioids, especially when there has been injection use, it is important to inform the person about what to expect, including symptoms and their duration. For example, withdrawal results in lower tolerance to opioids. This means that if the person resumes opioid use at

their usual dose after withdrawal they are at an increased risk of overdosing.

Due to these risks, withdrawal is best undertaken when there is a plan for admission to a residential rehabilitation or other psychosocial support programme. Alternatively, the person may be considered for opioid agonist maintenance treatment (OAMT) with either methadone or buprenorphine. Since withdrawal from opioids is associated with higher mortality than OAMT, the person's informed consent for opioid detoxification is needed.

In the community, stabilization on the dose of opioid agonist (methadone, buprenorphine) is first achieved, followed by gradual dose reduction, with additive medicines judiciously prescribed for withdrawal symptoms if and as needed *(6)*.

Opioid withdrawal can be managed by controlling the rate of cessation of opioids and by providing medication that relieves symptoms, or by a combination of the two.

Methadone is given orally at an initial dose of 15–20 mg, increasing, if necessary, to 30 mg per day. Then the dose is gradually decreased, until tapered off completely, over 3–10 days. As with buprenorphine, special care should be taken for individuals taking other sedating medicines *(1)*.

Buprenorphine is given sublingually at a dose range of 4–16 mg per day for 3–14 days for withdrawal management. Before initiating buprenorphine treatment, it is important to wait until signs and symptoms of opioid withdrawal become evident – at least eight hours after the last dose of heroin and 24–48 hours after the last dose of methadone; otherwise, there is a risk that buprenorphine itself will precipitate a withdrawal syndrome. Special care should be taken for individuals taking other sedating medicines *(1)*.

If opioid agonists are not available, use clonidine or lofexidine to manage some opioid withdrawal symptoms, namely hyperarousal. They are given at dose ranges of 0.1–0.15 mg three times daily orally and are dosed according to body weight. Lightheadedness and sedation may result. Monitor blood pressure closely *(1)*.

Other symptoms of withdrawal should also be treated, i.e. nausea with antiemetics, pain with simple analgesics, and insomnia with light sedatives (Table 6.7).

See Table 6.8 for further details on medication used in opioid withdrawal.

Table 6.7. Treatment of specific withdrawal symptoms *(3)*

Symptom	Medicine
Hyperarousal	Clonidine or lofexidine at doses of 0.1–0.15 mg three times daily by mouth, according to body weight Monitor blood pressure closely
Diarrhoea	Loperamide 4 mg then 2 mg after each loose stool Maximum 16 mg daily for up to five days
Nausea and vomiting	Metoclopramide 10 mg three times a day for a maximum of five days or prochlorperazine 5 mg three times a day or 12.5 mg IM twice a day
Abdominal cramps	Mebeverine 135 mg three times a day
Agitation, anxiety and insomnia	Diazepam up to 5–10 mg three times a day when required or zopiclone 7.5 mg at night for individuals with a history of benzodiazepine dependence
Muscular pains and headaches	Paracetamol, aspirin or non-steroidal anti-inflammatories

6.3.3 Pharmacological treatment of opioid dependence with opioid agonists (methadone, buprenorphine)

If the person is dependent on opioids, pharmacological treatment is generally more effective than withdrawal management *(6)*.

The treatment can include psychosocially assisted treatment with opioid agonists (methadone and buprenorphine) and antagonists (naltrexone).

OAMT requires the presence of an established and regulated national framework. It is characterized by the prescription of long-acting opioid agonists (or partial agonists), such as methadone or buprenorphine, generally on a daily, supervised basis as there is a high risk of misuse or diversion *(6)*.

The aims of OAMT are *(6)*:

- Reduce or eliminate unsupervised (medically) drug use.
- Reduce or prevent withdrawal symptoms.
- Reduce or stop intravenous use (and reduce associated risk of bloodborne virus transmission).
- Reduce overdose risk.
- Reduce criminal activity.
- Improve psychological and physical health and quality of life.
- Engage in treatment of other comorbid health conditions (HIV, hepatitis C, mental health conditions).
- Engage and provide an opportunity to work with the person and provide access to recovery management *(3)*.

OAMT combined with psychosocial interventions is the most effective treatment for opioid dependence. Methadone and buprenorphine are considered equally as effective as maintenance treatment. OAMT is indicated for all persons who are opioid-dependent and are able to give informed consent, and for whom there are no specific contraindications. OAMT can be continued for a few weeks to a very long period of time, depending on the clinical need. Some individuals are keen to go through withdrawal management after short periods of stability and others may decide on this after longer periods on OAMT *(6)*.

The decision on which to use is an individualized one based on the following:

- The person's preference.
- Their past experience of either option.
- Polysubstance use (especially comorbid benzodiazepine or alcohol dependence).
- Risk of diversion (medicine not being taken by the person it was prescribed for and being sold/given to others).
- Their long-term plans (including a preference for one or other as a detoxification regimen) *(3)*.

All individuals starting OAMT must be informed of the risks of toxicity and overdose, and the necessity for safe storage *(6)*.

Methadone

It is important to follow the general rule to "start low, go slow" when initiating methadone. Once inducted safely, the treatment's goal is to achieve an optimal dose for longer-term maintenance to prevent craving and the use of illicit opioids *(7)*.

The initial methadone dose should be 20 mg or less, depending on the level of opioid tolerance, allowing a high margin of safety to reduce inadvertent overdose. The dosage should then be quickly adjusted upwards if there are ongoing opioid withdrawal symptoms and downwards if there is any sedation. Increase the daily dose by 5–10 mg every few days if needed. The dose should be gradually increased to the point where illicit opioid use ceases; this is likely to be in the range of 60–120 mg methadone per day *(6)*.

Buprenorphine

Buprenorphine maintenance treatment should commence with a dose that is tailored to the pattern of opioid use, including the level of tolerance, the duration of action of opioids used and the timing of the most recent opioid use. The usual starting dose is 4 mg. From there, the dose should be increased (over days) to one that produces stable effects for 24 hours; this is generally in the range of 8–24 mg buprenorphine per day *(6)*.

Buprenorphine/naloxone combination

A combination product of buprenorphine and naloxone in a 4:1 ratio is available in two dose strengths (2 mg buprenorphine: 0.5 mg naloxone, and 8 mg buprenorphine:2 mg naloxone) *(6)*. It helps to prevent non-medical use of buprenorphine, including injecting or the diversion of buprenorphine tablets. This combination makes it less attractive for non-medical use, and its use may trigger withdrawal symptoms if injected *(7)*.

Table 6.8. Drug treatment of opioid dependence and withdrawal *(1)*

Medicine	Dose	Side-effects	Cautions
Methadone (to treat opioid withdrawal and dependence)	Opioid withdrawal: Methadone initial dose 15–20 mg, with a supplemental dose of 5–10 mg four hours later if necessary (up to 30 mg per day) Then gradually taper off over 3–10 days Opioid maintenance: Initial dose 10–20 mg with supplementary dose of 10 mg if needed, increasing the daily dose by 5–10 mg every few days if needed until the person is no longer experiencing opioid withdrawal and not using illicit opioids Maintain until ready to cease opioid agonist treatment	Sedation, confusion, nausea, vomiting, constipation, possible hormonal changes, decreased sex drive, ECG changes such as prolonged QT interval or bradycardia, hypotension, respiratory depression	Special care should be taken for individuals who are taking other sedating medicines Use with caution in persons with cardiac or respiratory disease
Buprenorphine (to treat opioid withdrawal and dependence)	Initial dose of 4–8 mg sublingually, increasing by 4–8 mg each day Use 4–16 mg per day for 3–14 days (as needed until the person is no longer experiencing opioid withdrawal and not using illicit opioids) Maintain at least 8 mg per day until ready to cease opioid agonist treatment	Sedation, dizziness, ataxia, nausea, vomiting, constipation, respiratory depression	Use with caution in persons with congestive heart failure, respiratory disease or liver disease Potential for abuse Abrupt cessation can cause withdrawal symptoms Special care should be taken for individuals who are taking other sedating medicines
Clonidine (alpha adrenergic agonist) (to treat opioid withdrawal)	0.1 mg 2–3 times daily. Increase as tolerated in divided doses to manage withdrawal symptoms. Maximum dose 1 mg daily.	Sedation, lightheadedness, dizziness, headache, nausea/vomiting, dry mouth, constipation, sexual dysfunction, depression, agitation, low blood pressure, tachycardia, sinus bradycardia, atrioventricular block	Use with caution in persons with cardiac, cerebrovascular and liver disease. Use lower doses in kidney disease. Be aware of the potential for abuse. Monitor vital signs closely DO NOT stop abruptly, as withdrawal can cause rebound hypertension
Lofexidine (alpha adrenergic agonist) (to treat opioid withdrawal)	Start 0.4–0.6 mg twice daily. Increase as needed by 0.4–0.8 mg daily Maximum single dose 0.8 mg. Maximum daily dose 2.4 mg (in 2–4 divided doses)	Sedation, lightheadedness, low blood pressure, ECG changes such as prolonged QT interval and sinus bradycardia	Use with caution in persons with cardiac, cerebrovascular and renal disease. Avoid in persons with prolonged QT syndrome, metabolic disarray or with other QT-prolonging medicines Monitor vital signs closely. DO NOT stop medicine abruptly, as withdrawal may cause rebound hypertension

6.3.4 Pharmacological treatment of opioid dependence with opioid antagonists (naltrexone)

Naltrexone is a highly specific opioid antagonist with a high affinity for opioid receptor sites. It has a very high affinity for opioid receptors and will displace heroin and methadone in minutes, and buprenorphine in 1–4 hours. It is used clinically after opioid withdrawal to prevent relapse to opioid dependence *(6)*.

Naltrexone has an effective duration of action of 24–48 hours, making it suitable for use once a day. Because it completely blocks the effects of heroin, naltrexone should be prescribed to those who are aiming at complete abstinence from opioids; this limits its use to a subpopulation of more motivated individuals following the completion of opioid withdrawal (Table 6.9) *(6)*.

Table 6.9. Medicine used to prevent relapse in opioid dependence *(1)*

Medicine	Dose	Side-effects	Cautions
Naltrexone	50 mg daily for 6–12 months. In opioid dependence, ensure that there has been no opioid use in the last seven days (e.g. by administration of a dose of naloxone)	Sedation, dizziness, nausea/vomiting, abdominal pain, insomnia, anxiety, reduced energy, joint and muscle pain If a person experiences gastrointestinal side-effects, these may be helped by reducing the dose to 25 mg naltrexone for a few days	Monitor liver function due to risk of liver toxicity Risk of FATAL OVERDOSE in persons who use opioids more than 24 hours after their last dose of naltrexone, due to the rapid loss of antagonistic effect DO NOT use in persons with liver failure or acute hepatitis

6.3.5 Special populations

Pregnant or breastfeeding women

A woman with an opioid use disorder should not be denied treatment with opioid agonist medication because of her pregnancy *(7)*.

Pregnant women dependent on opioids should be encouraged to use opioid maintenance treatment, whenever available, rather than to attempt opioid detoxification *(4)*.

Medical withdrawal from opioid agonists during pregnancy is not recommended *(7)*.

Mothers who are stable on opioid maintenance treatment with either methadone or buprenorphine should be encouraged to breastfeed unless the risks clearly outweigh the benefits *(4)*.

Methadone and buprenorphine can be used.

Do not use clonidine, acamprosate, disulfiram or naltrexone *(4)*.

Respiratory insufficiency

Methadone and buprenorphine may reduce respiratory drive *(3)*.

Renal or hepatic impairment

Use acamprosate with caution and at lower doses *(1)*.

Use naltrexone with caution. If feasible, liver function tests should be routinely carried out *(3)*.

Reduce dose or dosing frequency of methadone and buprenorphine.

HIV/AIDS, hepatitis and TB

For opioid-dependent persons with TB, hepatitis or HIV, opioid agonists should be administered in conjunction with other medical treatment; there is no need to wait for abstinence from opioids to commence anti-TB medication, treatment for hepatitis or antiretroviral medication *(6)*.

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MODULE 7
EPILEPSY

This section aims to help non-specialists manage epilepsy with convulsive seizures only.

Provide tailored information and support to people with epilepsy and their carers, according to their individual needs and circumstances. Include children and young people in discussions about their information and support needs, and provide information appropriate to their developmental age *(1)*.

Refer to the mhGAP guides (mhGAP-IG and mhGAP-HIG) for an overview of assessment and management including psychosocial interventions.

7.1 Educate the person/carers

- Epilepsy is a chronic condition, but if people take their medicine as prescribed in the majority of cases it can be fully controlled *(1)*.
- Take medicine at the same time every day to maintain consistent blood levels of the drug and to maximize its effectiveness *(2)*.
- Do not skip doses: skipping doses can increase the risk of seizures and decrease the effectiveness of the medication *(1)*.
- Suddenly stopping antiseizure medicines can be dangerous and can increase the risk of seizures *(2)*.

7.2 Select an antiseizure medicine

Choose a medicine based on its safety profile, availability, efficacy and cost-effectiveness.

Start with only one medicine at the lowest starting dose and increase the dose slowly until seizures are controlled (Table 7.1).

Discuss options for medicines, the importance of adherence to medicine and possible side-effects.

Develop an individualized treatment strategy with the person, and their family and carers if appropriate, taking into account:

- Sex.
- Age.
- Seizure type (generalized onset or focal onset seizures).
- Risks and benefits of antiseizure medicines.
- Possible interactions with any other medicines taken.
- Intellectual disabilities, hiv or other comorbidities.
- If the person is a woman or girl of childbearing potential.
- The preferences of the person, and their carers *(2)*.

Generalized onset seizures

- Offer monotherapy with lamotrigine or levetiracetam, or valproic acid (sodium valproate), as first-line treatment in boys/men and in women/girls who are not of childbearing potential *(2)*.
- Offer lamotrigine or levetiracetam as first-line monotherapy for generalized onset seizures in women and girls of childbearing potential. If the first choice is unsuccessful, offer the other of these options *(2)*.
- If lamotrigine, levetiracetam and valproic acid (sodium valproate) are not available for generalized onset seizures, consider monotherapy with either phenytoin or phenobarbital.
- If antiseizure medicine monotherapy is unsuccessful in people with generalized onset seizures, refer to a specialist for other treatment options *(1)*.

Focal onset seizures *(2)*

- Offer monotherapy with lamotrigine or levetiracetam as first-line treatment in children and adults with epilepsy.
- If the first choice is unsuccessful, offer carbamazepine as an alternate first-line monotherapy.
- Offer lacosamide as a second-line monotherapy if none of the first-line medicines is effective.
- If antiseizure medicine monotherapy is unsuccessful in people with focal onset seizures, refer to a specialist for other treatment options.

Monitor blood count, blood chemistry and liver function tests, if available.

For women of childbearing age or women considering pregnancy, consult a specialist.

Many anticonvulsants have interactions with other medicines. If this happens, consult a specialist *(1)*.

Table 7.1. Antiseizure medicines

Medicine	Dose	Maximum dose
Carbamazepine *(1)*	Adults: start 100–200 mg daily in 2–3 divided doses Increase by 200 mg each week	1400 mg daily
	Children: start 5 mg per kg daily in 2–3 divided doses Increase by 5 mg per kg daily each week	40 mg per kg daily OR 1400 mg daily
Valproic acid (sodium valproate) *(1)*	Adults: start 400 mg daily in two divided doses Increase by 500 mg daily each week	3000 mg daily
	Children: start 15–20 mg per kg daily in 2–3 divided doses Increase each week by 15 mg per kg daily	15–40 mg per kg daily
Phenobarbital *(1)*	Adults: start 60 mg daily in 1–2 divided doses Increase weekly by 2.5–5 mg (maximum)	180 mg daily
	Children: start 2–3 mg per kg daily in two divided doses Increase weekly by 1–2 mg per kg daily depending on tolerance	6 mg daily
Phenytoin *(1)*	Adults: start 150–200 mg daily in two divided doses Increase by 50 mg daily every 3–4 weeks	400 mg daily
	Children: start 3–4 mg per kg daily in two divided doses Increase by 5 mg per kg daily every 3–4 weeks	300 mg per day
Lamotrigine *(3)*	Initially 25 mg once daily for 14 days, then increase to 50 mg once daily for a further 14 days, then increase in steps of up to 100 mg every 7–14 days; maintenance 100–200 mg daily in 1–2 divided doses Lamotrigine should not be taken by anyone younger than 16 years of age	500 mg
Levetiracetam *(3)*	Initially 250 mg twice daily, then increased in steps of 500 mg twice daily Dose to be increased every 2–4 weeks	1.5 g twice daily

7.3 Monitor treatment

Evaluate side-effects of medicine, including adverse effects and idiosyncratic reactions (clinically and with appropriate laboratory tests when available) (Table 7.2).

If the person is not improving on the current dose:

- Review adherence to medicine.
- Consider an increase in medicine dose as needed to the maximal dose, if there are no adverse effects.
- If response is still poor, consider switching medicine. The new medicine should be at an optimum dose before the first is slowly discontinued.
- Follow up should occur every 3–6 months *(1)*.

7.4 Refer to a specialist *(1)*:

- If seizures are not controlled despite good compliance (after trying two anticonvulsant medicines in adequate doses).
- If seizures are not fully controlled with a single medicine.
- In cases of pregnant women.
- In cases of children with epilepsy.
- In cases of comorbid mental or physical health problems.
- Before stopping antiseizure medicines.

Table 7.2. Side-effects of antiseizure medicines

Medicine	Common side-effects	Serious side-effects	Cautions/contraindications *(see section 7.7 for special populations)*
Carbamazepine *(1)*	Sedation, confusion, dizziness, ataxia, double vision, nausea, diarrhoea, leukopenia	Hepatotoxicity, cardiac conduction delay, low sodium levels	Caution in persons with history of blood disorders, kidney, liver or cardiac disease Dose may need to be adjusted after two weeks due to induction of its own metabolism
Valproic acid (sodium valproate)	Sedation, headache, tremor, ataxia, nausea, vomiting, diarrhoea, weight gain, transient hair loss *(1)*	Impaired hepatic function, thrombocytopenia, leukopenia, drowsiness/ confusion (valproate-induced hyperammonaemic encephalopathy, a sign of toxicity), liver failure, haemorrhagic pancreatitis *(1)*	Contraindicated in women and girls of childbearing potential owing to the high risk of birth defects and developmental disorders *(4)* Use with caution if underlying or suspected hepatic disease *(4)* Drug–drug interactions: sodium valproate levels are decreased by carbamazepine, increased by aspirin *(4)*
Phenobarbital *(1)*	Sedation, hyperactivity in children, ataxia, nystagmus, sexual dysfunction, depression and risk of dependence	Liver failure (hypersensitivity reaction), decreased bone mineral density	Contraindicated in acute intermittent porphyria Lower doses for persons with kidney or liver disease
Phenytoin *(1)*	Sedation, confusion, dizziness, tremor, motor twitching, ataxia, double vision, nystagmus, slurred speech, nausea, vomiting, constipation	Haematologic abnormalities, hepatitis, polyneuropathy, gum hypertrophy, acne, lymphadenopathy, increase in suicidal ideation	Lower doses for persons with kidney or liver disease
Lamotrigine *(3)*	Aggression, agitation, arthralgia, diarrhoea, dizziness, drowsiness, dry mouth, rash, fatigue, headache, irritability, nausea, pain, sleep disorders, tremor	Severe rash, facial oedema	Serious skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, have developed (especially in children)
Levetiracetam *(3)*	Drowsiness, dizziness, ataxia, diplopia, memory impairment, apathy, paraesthesia	Behavioural disturbances, hallucinations	Avoid in women who are pregnant or breastfeeding
	Rarely: Antiepileptics can cause severe bone marrow depression, hypersensitivity reactions including Stevens-Johnson syndrome, altered vitamin D metabolism and vitamin K-deficient haemorrhagic disease of newborns		

7.5 When and how to stop antiseizure medicine

In children and adults with epilepsy, after a person has been seizure-free for two years, discontinuation of antiseizure medicine may be considered. This decision is made after consideration of relevant clinical, social and personal factors and with the involvement of the person and the family *(1)*.

The plan should include reducing their antiseizure medicines gradually:

- For most medicines, this would typically be over at least three months.
- For benzodiazepines and barbiturates, this would typically be over a longer period to reduce the risk of drug-related withdrawal symptoms.
- For people with epilepsy taking multiple antiseizure medicines, medicines should be discontinued one at a time.
- If seizures recur during or after discontinuation, reverse the last dose reduction and seek guidance from a specialist *(2)*.

7.6 Emergency management

Do not leave the person alone.

Do not put anything in the mouth.

Make sure that the person is in a safe place and, if possible, put them on their side to help breathing; loosen any neckties or clothing around the neck, take off eyeglasses and place something soft under the head (if available) *(1)*.

Check airway, breathing and circulation.

Ensure that the person has nothing in their airway, is breathing well and has a stable pulse.

Check blood pressure, temperature and respiratory rate.

Start timing the duration of the convulsions, if possible.

Place an intravenous line for medicine/fluid administration if possible (Table 7.3) *(1)*.

Table 7.3. Emergency medicine *(1)*

If IV line is established	Normal saline administration slowly 30 drops per minute Glucose IV Adults: 25–50 ml of 50% Children: 2–5 ml per kg of 10%	Diazepam IV Adults: 10 mg Children: 1 mg per year of age OR Lorazepam IV Adults: 4 mg Children: 0.1 mg per kg
If IV line is not established		Diazepam rectally Adults: 10 mg Children: 1 mg per year of age OR Midazolam buccally/intranasally Adults: 5–10 mg Children: 0.2 mg per kg

Note: if the convulsions have not stopped within 10 minutes of the first dose of emergency medicine, then give the second dose. Do not give more than two doses of emergency medicine

If the convulsions do not stop, refer the person to a specialist.

Also immediately refer a person with possible head injury, neuroinfection (fever) or focal deficits (e.g. tumour) *(1)*.

For status epilepticus (i.e. seizures persisting after two doses of benzodiazepines):

- Continue to check airway, breathing and circulation.
- Give oxygen; monitor need for intubation/ventilation continuously.
- Prevent physical harm or injury.
- Be aware of the possible underlying causes of status epilepticus, including hypoglycaemia, eclampsia and alcohol withdrawal, which may need to be treated with additional medicine *(5)*.
- Be alert to non-adherence to antiseizure medicines, which can also be a cause of status epilepticus *(5)*.
- The choice of these medicines (see table 7.4) Depends on local resource settings, including availability and facilities for monitoring.

Table 7.4. Medicines for status epilepticus

Medicine	Dose	Maximum dose
Valproic acid (sodium valproate) IV *(1)*	20 mg per kg over 30 minutes	1 g
Phenobarbital IV or IM *(1)*	15–20 mg per kg at a maximal rate of 100 mg per minute	1 g
Phenytoin IV *(1)*	15–20 mg per kg over 60 minutes	1 g
Levetiracetam IV *(5)*	60 mg per kg over 10 minutes	4500 mg
Fosphenytoin IV* *(6)*	15–20 mg phenytoin sodium equivalents (PE) per kg IV at a rate of 100–150 mg PE per kg	1.5 g

*Fosphenytoin sodium 1.5 mg = phenytoin sodium 1 mg.

Note: the maximal rate of IV administration should not be exceeded due to cardiovascular risk associated with rapid infusion rates.

7.7 Special populations

People with intellectual disability

- The choice of antiepileptic drug treatment in individuals with intellectual disability and epilepsy depends on the type of seizure and should be individualized.
- When available, offer either valproic acid or carbamazepine instead of phenytoin or phenobarbital due to lower risk of behavioural adverse effects.

Older adults

- Use lower doses in older adults as they are more likely to have comorbid medical conditions, take multiple medicines, have decreased hepatic and renal clearance and are more sensitive to side-effects.

Women of reproductive age

- Refer women and girls with epilepsy who are planning pregnancy or are pregnant to a specialist, if available. Discuss the relative benefits and risks of adjusting drug treatment with the woman or girl planning a pregnancy to enable her to make informed decisions. This should include discussing the balance between the risks of poorly controlled seizures and the risks to the baby when antiseizure medicines are taken in pregnancy or while breastfeeding *(2)*.
- Use lamotrigine and levetiracetam in this population *(1)*.
- Do not prescribe valproic acid (sodium valproate) in women and girls of childbearing potential owing to the high risk of birth defects and developmental disorders in children exposed to it in the womb *(4)*.
- Women and girls of childbearing potential who are prescribed valproic acid (sodium valproate) should be advised to use effective contraception *(2)*.
- If a woman taking valproic acid (sodium valproate) is planning to become pregnant or becomes pregnant, refer to a specialist trained in the management of epilepsy in pregnant women. Every effort should be made to switch from sodium valproate to appropriate alternative treatment prior to conception. If switching is not possible, the woman should receive further counselling regarding the risks of this medicine for the unborn child to support her in informed decision-making *(2)*.
- Avoid phenytoin.
- Use carbamazepine with caution, and after informed consultation with the person and carers.
- Advise folate (5 mg per day) to prevent neural tube defects in ALL women of childbearing age *(1)*.

Pregnant women

- Avoid polytherapy. Multiple medicines in combination increase the risk of teratogenic effects during pregnancy *(1)*.
- If medicine is stopped during pregnancy, always taper off slowly.
- Advise delivery in hospital.
- At delivery, give intramuscular vitamin K (1 mg) to the newborn to prevent haemorrhagic disease *(1)*.

Breastfeeding women *(1)*

- Women with epilepsy taking antiseizure medicines (phenobarbital, phenytoin, valproic acid (sodium valproate), carbamazepine, lamotrigine, levetiracetam, topiramate, lacosamide) may continue their medication.

Persons living with HIV

- For individuals taking antiretroviral therapy, it is preferable to avoid medicines that induce hepatic cytochrome P-450 enzymes. Therefore, avoid phenytoin and carbamazepine when possible.
- Sodium valproate is preferred as it has fewer drug–drug interactions *(2)*.
- Sodium valproate is to be avoided in women with HIV *(2)*.

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ANNEXES

ANNEX I. ESSENTIAL MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS

The WHO Model List of Essential Medicines (EML) presents a list of minimum medicine needs for a basic health care system, containing the most efficacious, safe and cost-effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment. The EML also indicates therapeutic alternatives to listed medicines that may be considered for selection in national essential medicines lists.

The EML is updated every two years; the 2023 list can be found on the following website:
https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.02

A summary of the medicines for mental and behavioural conditions is provided in the table below. The square box symbol (□) is intended to indicate the therapeutic alternatives. The complementary lists present essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. In case of doubt, medicines may also be listed as complementary on the basis of consistent higher costs or less attractive cost-effectiveness in a variety of settings.

Medicines for depressive disorders	
Amitriptyline	Tablet: 25 mg; 75 mg (as hydrochloride).
□ Fluoxetine Therapeutic alternatives: - Citalopram - Escitalopram - Fluvoxamine - Paroxetine - Sertraline	Solid oral dosage form: 20 mg (as hydrochloride).
Medicines for anxiety disorders	
□ Diazepam* Therapeutic alternatives: - Lorazepam	Tablet (scored): 2 mg; 5 mg. *For short-term emergency management of acute and severe anxiety symptoms only.
□ Fluoxetine Therapeutic alternatives: - Citalopram - Escitalopram - Fluvoxamine - Paroxetine - Sertraline	Solid oral dosage form: 20 mg (as hydrochloride).
Medicines for psychotic disorders	
□ Fluphenazine Therapeutic alternatives: - Haloperidol decanoate - Zuclopenthixol decanoate	Injection: 25 mg (decanoate or enantate) in 1 mL ampoule.
□ Haloperidol Therapeutic alternatives: - Chlorpromazine	Tablet: 2 mg; 5 mg.
Haloperidol	Injection: 5 mg/mL in 1 mL ampoule.
Olanzapine	Powder for injection: 10 mg in vial.
□ Paliperidone Therapeutic alternatives: - Risperidone injection	Injection (prolonged-release): 25 mg; 50 mg; 75 mg; 100 mg; 150 mg (as palmitate) in pre-filled syringe.

□ Risperidone Therapeutic alternatives: - Aripiprazole - Olanzapine - Paliperidone - Quetiapine	Solid oral dosage form: 0.25 mg to 6.0 mg.
Complementary list	
Clozapine	*Solid oral dosage form: 25 to 200 mg.*
Medicines for bipolar disorders	
□ Carbamazepine	Tablet (scored): 100 mg; 200 mg; 400 mg.
Lithium carbonate	Solid oral dosage form: 300 mg.
□ Quetiapine	Tablet (immediate-release): 25 mg; 100 mg; 150 mg; 200 mg; 300 mg.
Therapeutic alternatives: - Aripiprazole - Olanzapine - Paliperidone	Tablet (modified-release): 50 mg; 150 mg; 200 mg; 300 mg; 400 mg.
Medicines for disorders due to psychoactive substance use	
Medicines for alcohol use disorders	
Acamprosate calcium	Tablet: 333 mg
Naltrexone	Injection suspension (extended-release): 380 mg in vial. Tablet: 50 mg.
Medicines for nicotine use disorders	
Bupropion	Tablet (sustained-release): 150 mg (hydrochloride).
Nicotine replacement therapy	Chewing gum: 2 mg; 4 mg (as polacrilex). Lozenge: 2 mg; 4 mg. Oral spray: 1 mg per actuation. Transdermal patch: 5 mg to 30 mg/16 hours; 7 mg to 21 mg/24 hours.
Varenicline	Tablet: 0.5 mg, 1 mg.
Medicines for opioid use disorders	
Complementary list	
□ *Methadone** *Therapeutic alternatives:* *- Buprenorphine*	*Concentrate for oral liquid: 5 mg/mL; 10 mg/mL (hydrochloride). Oral liquid: 5 mg/5 mL; 10 mg/5 mL (hydrochloride).* **The medicines should only be used within an established support programme.*
Antiseizure medicines	
Carbamazepine	Oral liquid: 100 mg/5 mL. Tablet (chewable): 100 mg; 200 mg. Tablet (scored): 100 mg; 200 mg; 400 mg.
Diazepam	Rectal gel: 5 mg/mL in 0.5 mL, 2 mL, 4 mL rectal delivery system. Rectal solution: 2 mg/mL in 1.25 mL, 2.5 mL rectal tube; 4 mg/mL in 2.5 mL rectal tube.
Lamotrigine*	Tablet: 25 mg; 50 mg; 100 mg; 200 mg. Tablet (chewable, dispersible): 2 mg; 5 mg; 25 mg; 50 mg; 100 mg; 200 mg. *For use as adjunctive therapy for treatment-resistant partial or generalized seizures.
Levetiracetam	Oral solution: 100 mg/mL. Tablet: 250 mg; 500 mg; 750 mg; 1000 mg.

□ Lorazepam Therapeutic alternatives: - Diazepam (injection) - Midazolam (injection)	Injection: 2 mg/mL in 1 mL ampoule; 4 mg/mL in 1 mL ampoule.
Magnesium sulfate*	Injection: 0.5 g/mL in 2 mL ampoule (equivalent to 1 g in 2 mL; 50% weight/volume); 0.5 g/mL in 10 mL ampoule (equivalent to 5 g in 10 mL; 50% weight/volume). *For use in eclampsia and severe pre-eclampsia and not for other convulsant disorders.
Midazolam	Solution for oromucosal administration: 5 mg/mL in 0.5 mL, 1 mL, 1.5 mL, 2 mL pre-filled syringe; 10 mg/mL in 0.25 mL, 0.5 mL, 0.75 mL, 1 mL pre-filled syringe. Injection:*1 mg/mL in 5 mL vial; 5 mg/mL in 1 mL or 3 mL vial. *For buccal administration when solution for oromucosal administration is not available.
Phenobarbital	Injection: 30 mg/mL or 60 mg/mL,* 200 mg/mL (sodium). Oral liquid: 15 mg/5 mL. Tablet: 15 mg to 100 mg. *There is a specific indication for restricting its use to children.
Phenytoin	Injection: 50 mg/mL (phenytoin sodium). Oral liquid: 30 mg/5 mL (phenytoin). Solid oral dosage form: 25 mg; 50 mg; 100 mg (phenytoin sodium). Tablet (chewable): 50 mg (phenytoin).
Valproic acid (sodium valproate)* *Avoid use in pregnancy and in women and girls of childbearing potential, unless alternative treatments are ineffective or not tolerated, because of the high risk of birth defects and developmental disorders in children exposed to valproate in the womb.	Oral liquid: 200 mg/5 mL. Tablet (crushable): 100 mg. Tablet (enteric-coated): 200 mg; 500 mg.
Complementary list	
Ethosuximide	*Capsule: 250 mg.* *Oral liquid: 250 mg/5 mL.*
Levetiracetam	*Concentrate solution for infusion: 500 mg/5mL in 5 mL vial.* *Solution for infusion: 5 mg/mL; 10 mg/mL; 15 mg/mL in 100 mL bag.*
*Valproic acid (sodium valproate)** **Avoid use in pregnancy and in women and girls of childbearing potential, unless alternative treatments are ineffective or not tolerated, because of the high risk of birth defects and developmental disorders in children exposed to valproate in the womb.*	*Injection: 100 mg/mL in 3 mL, 4 mL, 10 mL ampoule.*

ANNEX II. COMMON DRUG–DRUG INTERACTIONS WITH MEDICINES USED FOR MENTAL AND BEHAVIOURAL DISORDERS

Medicines for depression and anxiety disorders		
Tricyclic antidepressants (TCAs)	Antihypertensives and other drugs that block α1 receptors	TCAs are adrenergic α1 blockers and cause postural hypotension. This effect can be exacerbated, resulting in falls.
TCAs	Anticholinergic drugs such as antihistamines or antipsychotics with anticholinergic effects, such as chlorpromazine	TCAs are anticholinergic (dry mouth, blurred vision, constipation). This effect can be exacerbated, resulting in cognitive impairment and gastrointestinal obstruction.
TCAs	Benzodiazepines	Increased sedation.
TCAs	Lithium Sodium valproate	Increased risk of weight gain.
TCAs: amitriptyline	Antimalarial quinine	Levels of amitriptyline may be increased.
TCAs with marked serotonin reuptake inhibition (e.g. imipramine and clomipramine*)	Selective serotonin reuptake inhibitors (SSRIs) Monoamine oxidase inhibitors	Risk of serotonin syndrome.
TCAs	Cimetidine	Increased blood levels and side-effects of TCAs.
TCAs	Alcohol	Increased sedation and drowsiness
**Note that clomipramine has the same interaction profile as amitriptyline.*		
SSRIs	Aspirin and nonsteroidal anti-inflammatory medicines	SSRIs inhibit platelet aggregation. This effect can be exacerbated, resulting in risk of bleeding, particularly of the upper gastrointestinal tract.
SSRIs	Diuretics	SSRIs are likely to cause hyponatraemia. This effect may be exacerbated, resulting in electrolyte disturbances.
SSRIs	Benzodiazepines	Causes higher serum levels of benzodiazepines.
Fluoxetine	Tamoxifen, codeine and tramadol	Reduces the effect of these drugs.
Fluoxetine	Warfarin	Increased risk of bleeding.
SSRIs: - Fluoxetine - Fluvoxamine	Haloperidol	Increase the concentration of haloperidol.
Fluoxetine	Carbamazepine	Increases the levels of carbamazepine.
Benzodiazepines	Methadone	Use with caution.
Benzodiazepines	Alcohol	Sedation is increased by 20–30%.
Benzodiazepines	Clozapine	Sedation and hypotension are increased.
Benzodiazepines	Levodopa	The effect of levodopa is reduced.
Medicines used for psychoses		
Chlorpromazine	Antihypertensives	Increases effects of blood pressure-lowering drug treatments.
Chlorpromazine	Epinephrine	Lowers blood pressure if combined with epinephrine.
Chlorpromazine	Quinine	Levels may be increased by antimalarials including quinine.
Fluphenazine	Antihypertensives	Increases effects of blood pressure-lowering drug treatments.
Fluphenazine	Epinephrine	Can lower blood pressure if used with epinephrine.

Medicines for bipolar disorder		
Lithium	Angiotensin-converting inhibitors enzyme inhibitors	Lithium toxicity may be increased.
Lithium	Thiazide diuretics	Renal clearance of lithium is reduced, and levels increased within a few days.
Lithium	Nonsteroidal anti-inflammatory medicines	Lithium levels should be frequently monitored.
Lithium	Methyldopa	Lithium levels may be increased.
Lithium	Metronidazole Tetracycline	Lithium levels may be increased.
Lithium	Carbamazepine	Neurotoxicity reported (rarely).
Sodium valproate	Antipsychotics	The anticonvulsant effect of sodium valproate is antagonized by drugs that lower the seizure threshold e.g. antipsychotics. Weight gain can be exacerbated by other drugs such as clozapine and olanzapine.
Medicines used for epilepsy		
Carbamazepine - Phenobarbital - Phenytoin	Haloperidol	Decrease the concentration of haloperidol.
Carbamazepine	Diltiazem Erythromycin Influenza vaccine Isoniazid Verapamil	Carbamazepine levels can be increased.
Carbamazepine	Phenobarbital Phenytoin Primidone Theophylline TCAs	Carbamazepine levels can be decreased.
Carbamazepine	Most antidepressants Most antipsychotics Benzodiazepines Sodium valproate Warfarin Zolpidem Some cholinesterase inhibitors Methadone Thyroxine Theophylline Oestrogen preparations Other steroids Hormonal birth control Immunosuppressants Antiepileptics Some antiretrovirals	Carbamazepine may decrease plasma levels or effects of these drugs. Carbamazepine is a potent inducer of hepatic cytochrome enzymes. Plasma levels of most antidepressants, most antipsychotics, benzodiazepines, warfarin, zolpidem, some cholinesterase inhibitors, methadone, thyroxine, theophylline, oestrogens and other steroids may be reduced by carbamazepine, resulting in treatment failure.
Sodium valproate	Aspirin Erythromycin Fluoxetine Cimetidine	Plasma levels of sodium valproate can be increased.

Sodium valproate	TCAs, particularly: Clomipramine Lamotrigine Warfarin Phenobarbital	Sodium valproate can increase the plasma levels of these drugs.
Sodium valproate	Olanzapine	Sodium valproate may significantly lower plasma concentrations of olanzapine.
Antiseizure medicines	Used in combination	May increase or reduce the effect of other antiepileptics. Reduce the effect of: hormonal birth control immunosuppressants, antipsychotics, methadone, some antiretrovirals.
Medicines used for dementia		
Donepezil	Ketoconazole Itraconazole Erythromycin Quinidine Fluoxetine Paroxetine	Plasma levels of donepezil may be increased by these drugs.
Donepezil	Rifampicin Phenytoin Carbamazepine Alcohol	Plasma levels of donepezil may be decreased by these drugs.
Acetylcholinesterase inhibitors	Anticholinergic drugs Competitive neuromuscular blockers (e.g. tubocurarine)	Acetylcholinesterase inhibitors decrease the effect of these drugs.
Acetylcholinesterase inhibitors	Cholinomimetics such as neuromuscular blocking agents (e.g. succinylcholine), cholinergic agonists and peripherally acting cholinesterase inhibitors, e.g. neostigmine.	Acetylcholinesterase inhibitors increase the effect of these drugs.
Acetylcholinesterase inhibitors	Beta blockers Amiodarone Calcium channel blockers	Effects on cardiac conduction, such as bradycardia, atrioventricular block and arterial hypotension. Caution with drugs known to induce QT prolongation and/or torsade de pointes.
Acetylcholinesterase inhibitors	Antipsychotics	Movement disorders and neuroleptic malignant syndrome reported.
Acetylcholinesterase inhibitors	Seizure-lowering agents	May result in reduced seizure threshold because of the electrolyte abnormalities associated with acetylcholinesterase inhibitors.
Memantine	L-dopa Dopaminergic agonists Selegiline Anticholinergics	Effects of these drugs may be increased.
Memantine	Barbiturates Antipsychotics	Effects of these drugs may be reduced.
Memantine	Amantadine Ketamine Dextromethorphan	Increased risk of central nervous system toxicity.
Memantine	Antispasmodic agents Dantrolene or baclofen	Dosage adjustment may be necessary.

Medicines used for disorders due to substance use		
Methadone	Carbamazepine Phenytoin	Decreased methadone levels.
Methadone	Fluoxetine	Increased levels of methadone.
Methadone	Atypical antipsychotics (aripiprazole, clozapine, olanzapine, quetiapine, risperidone)	Increased sedative effect.
Methadone	Benzodiazepines and hypnotics	Increased sedative effect.
Disulfiram	Alcohol	Throbbing headache, facial flushing, nausea, vomiting, tachycardia, hypotension, dyspnoea, blurred vision, weakness and confusion.
Disulfiram	Warfarin	Increased prothrombin time.