

## **4 CENTRAL NERVOUS SYSTEM**

### **4.01 HYPNOTICS & ANXIOLYTICS**

#### **WHO MODEL FORMULARY 2004 NOTES:**

The most widely used anxiolytics and hypnotics are the benzodiazepines. Treatment of anxiety should be limited to the lowest effective dose for the shortest possible time. The cause of insomnia should be established and appropriate treatment for underlying factors instituted before hypnotics are considered. Hypnotics may be of value for a few days but rarely longer than a week.

Tolerance and dependence (both physical and psychological) and subsequent difficulty in withdrawing the drug may occur after regular use for more than a few weeks. Patients with chronic anxiety, alcohol or drug dependence or those with personality disorders are more likely to become dependent. Anxiolytics and hypnotics should be prescribed in carefully individualized dosage and use should be limited to control of acute conditions such as panic attacks and acute anxiety and severe, incapacitating insomnia. There is usually no justification for prolonging treatment with anxiolytics and hypnotics for more than one to two weeks.

If used for longer periods, withdrawal should be gradual by reduction of the dose over a period of weeks or months, as abrupt discontinuation may produce confusion, toxic psychosis, convulsions or a condition resembling delirium tremens. The benzodiazepine withdrawal syndrome may develop at any time up to 3 weeks after stopping a long-acting benzodiazepine but may occur within a few hours in the case of a short-acting one. The syndrome is characterized by insomnia, anxiety, loss of appetite and body-weight, tremor, perspiration, tinnitus and perceptual disturbances. These symptoms may be similar to the original complaint and encourage further prescribing. Some symptoms may continue for weeks or months after stopping benzodiazepines.

Patients should be warned that their ability to drive or operate machinery may be impaired and that the effects of alcohol may be enhanced.

---

GENERIC (TRADE) NAME	CAT.	INDICATION/DOSE
<b>Diazepam Tab 5mg (Valium)</b>	<b>PS</b> MSL  EML	<i>By mouth</i> , Anxiety Adult 2mg 3 times daily max 30mg/DAY in divided doses; Elderly half adult dose. Insomnia (anxiety-linked) Adult 5-15mg at bedtime. Spastic conditions: Adult 2.5-15mg daily in divided doses, max 60mg/DAY; Child 2-40mg/DAY. Sedation/premedication see chapter 13 Anaesthetics section 13.06.
<b>Diazepam Inj 5mg/ml, 2ml (Valium)</b>  <b>Avoid IM route - unreliable absorption.</b>	<b>PS</b> MSL  EML	<i>By slow IV inj</i> undiluted over 2-4 minutes into a large vein. Severe acute anxiety (under close observation): Adult 10-20mg, repeat if needed after 4 hours.
<b>Lorazepam Tab 1mg (Ativan/Temesta)</b>	<b>PS</b>  EML	<i>By mouth</i> , Anxiety: Adult 1-4mg daily in divided doses; Elderly half dose. Insomnia (anxiety-linked, short term use): Adult 1-2mg at night.
<b>Zolpidem Tab 10mg (Stilnox)</b>	<b>PS</b> D	<i>By mouth</i> , Insomnia: Adult 10mg at bedtime; Elderly or debilitated 5mg.
<b>PS</b> – Drugs subject to international control under the Convention on Psychotropic Substances (1971).		

**COMMENT/CAUTIONS:**

- **PS Psychotropic Substances.** Recording required in pharmacy/ward/OR.
- It is recommended that benzodiazepines be used for **short-term relief** (around 2-4 weeks) of anxiety that is severe, disabling or subjecting the individual to unacceptable distress.
- All hypnotics/anxiolytics should be prescribed “as needed” as far as possible.
- **Long acting benzodiazepines** such as diazepam should not be used for insomnia especially in the elderly where they may give rise to memory and co-ordination problems.  
**Withdrawal:** To withdraw from chronic benzodiazepine therapy, transfer patient to an equivalent dose of diazepam if possible (e.g. diazepam 5mg = lorazepam 2.5mg = midazolam 7.5mg), then reduce in steps of one-eighth of the daily dose every 2 weeks.
- **Adverse effects:** drowsiness, light-headedness, confusion, ataxia, dependence, vertigo, GI disturbances, respiratory depression (NOTE for **midazolam**). Patients should be warned that their ability to drive or operate machinery may be impaired and that the effects of alcohol may be enhanced.

## 4.02 ANTIPSYCHOTIC MEDICINES

### WHO MODEL FORMULARY 2004 NOTES:

Treatment of psychotic disorders is both pharmacological and psychosocial. Individual and community programmes for relearning old skills and developing new ones and for learning to cope with the illness should be initiated. Classes of antipsychotic drugs include phenothiazines (e.g. chlorpromazine), butyrophenones (for example haloperidol), thioxanthenes (e.g. flupentixol) and newer 'atypical' neuroleptics including clozapine and risperidone. The various antipsychotic drugs do not, in general, differ in their antipsychotic activity, but differ in range and quality of adverse effects (see below).

**ADVERSE EFFECTS.** Very common with long-term administration of antipsychotic medicines. Hypotension and interference with temperature regulation, neuroleptic malignant syndrome and bone-marrow depression are the most life-threatening. Hypotension and interference with temperature regulation are dose-related. They can result in dangerous falls and hypothermia in the elderly and this must be considered before prescribing these drugs for > 70 yo.

Extrapyramidal symptoms are the most troublesome and are caused most frequently by the piperazine phenothiazines (e.g. fluphenazine), butyrophenones (e.g. haloperidol) and the depot preparations. Although easily recognized, they are not so easy to predict because they depend in part on the dose and patient susceptibility as well as the type of drug. However, there is a general tendency for low-potency drugs to have less extrapyramidal adverse effects, while high-potency drugs such as haloperidol have more extrapyramidal effects but less sedation and anticholinergic (more correctly antimuscarinic) effects. Sedation and anticholinergic effects usually diminish with continued use. Extrapyramidal symptoms consist of parkinsonian-type symptoms including tremor which may occur gradually; dystonia (abnormal face and body movements) and dyskinesia, which may appear after only a few doses; akathisia (restlessness), which may occur after large initial doses and may resemble an exacerbation of the condition being treated; and tardive dyskinesia (an orofacial dyskinesia), which usually takes longer to develop but may develop on short-term treatment with low doses; short-lived tardive dyskinesia may occur after withdrawal of the drug. Parkinsonian symptoms are usually reversible on withdrawal of the drug and may be suppressed by anticholinergic (antimuscarinic) drugs but they may unmask or worsen tardive dyskinesia. Tardive dyskinesia is usually associated with long-term treatment and high dosage, particularly in elderly patients. There is no established treatment for tardive dyskinesias, which may be irreversible on withdrawing therapy. However, withdrawal at the earliest signs of tardive dyskinesia may halt its full development. Treatment of all patients on antipsychotics must be carefully and regularly reviewed.



### 4.03 ANTIDEPRESSANTS

#### WHO MODEL FORMULARY 2004 NOTES:

Tricyclic and related antidepressants and the more recently introduced selective serotonin reuptake inhibitors (SSRIs) are the most widely used drugs in the treatment of depressive disorders. The response to antidepressant therapy is usually delayed with a lag-period of up to two weeks and at least six weeks before maximum improvement occurs. It is important to use doses that are sufficiently high for effective treatment, but not so high as to cause toxic effects. Low doses should be used for initial treatment in the elderly. The use of more than one antidepressant at a time is not recommended since this does not enhance effectiveness and may result in enhanced adverse effects/interactions.

Patients should be reviewed every 1-2 weeks at the start of treatment. Treatment should be continued for at least 4 weeks (6 weeks in the elderly) before considering whether to change to another antidepressant due to lack of efficacy. In the case of a partial response, treatment may be continued for a further 2 weeks (elderly patients may take longer to respond). Remission usually occurs after 3-12 months. Treatment at full therapeutic dose should be continued for at least 4-6 months after resolution of symptoms (about 12 months in the elderly). Treatment should not be withdrawn prematurely otherwise symptoms are likely to recur. Patients with a history of recurrent depression should continue to receive maintenance treatment (for at least 5 years and possibly indefinitely). Lithium [not on Mercy Ships list] may be used as an alternative for maintenance treatment. Reduction in dose should be gradually carried out over a period of about 4 weeks or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment).

Tricyclic and related antidepressants can be divided into those with more or less sedative effect. Those with sedative properties include **amitriptyline** and those with less sedative effects include imipramine. These drugs are most effective in the treatment of depression associated with psychomotor and physiological disturbances. Adverse effects include anticholinergic (more correctly antimuscarinic) symptoms of dry mouth, blurred vision, constipation and urinary retention. Arrhythmias and heart block can occur. Minimal quantities of tricyclic antidepressants should be prescribed at any one time (dangerous in overdose).

The SSRIs characteristically cause GI/sleep disturbances and hypersensitivity reactions including rash (may be a sign of an impending serious systemic reaction and discontinuation should be considered) but they are less sedating and have fewer anticholinergic (antimuscarinic) and cardiotoxic effects than tricyclic antidepressants. SSRIs are less toxic in overdose than the older tricyclic compounds. They may be preferred in patients in whom the risk of suicide is strong, but there is some concern that SSRIs may increase suicidal ideation.

---

#### 4.03a TRICYCLIC ANTIDEPRESSANTS [TCA]

[NOTE: Antidepressants may take at least TWO weeks to give effect, counsel patients accordingly to encourage compliance and avoid unreasonable expectations and disappointment.]

GENERIC (TRADE) NAME	CAT.	INDICATION/DOSE
<b>Amitriptyline Hydrochloride Tab 25mg (Laroxyl)</b>	EML	Depression: <i>by mouth</i> Adult initially 75mg daily in divided doses <i>or</i> as a single dose at bedtime increased gradually as needed to 150-200mg daily (Elderly/adolescents half dose); not recommended in under 16 yo.

#### COMMENT/CAUTIONS:

- **Contraindications:** recent MI, arrhythmias (especially heart block); manic phase in bipolar disorders; severe liver disease; children; porphyria.
- **Adverse effects:** dry mouth, blurred vision, constipation, urinary retention. May cause drowsiness: caution patients to avoid driving/operate machinery.
- Do not use **TCAs** combined with **MAOIs** [Monoamine-oxidase inhibitor, none on the Mercy Ships list] unless under specialist supervision.

#### 4.03b SELECTIVE SEROTONIN REUPTAKE INHIBITORS [SSRI]

GENERIC (TRADE) NAME	CAT.	INDICATION/DOSE
<b>Fluoxetine Cap 20mg (Prozac) [SSRI]</b>		Depression: <i>by mouth</i> Adult 20mg in the morning; child not recommended

#### COMMENT/CAUTIONS:

- A drug-free gap of ONE WEEK should be left after stopping **SSRI** (TWO WEEKS for paroxetine or sertraline, FIVE WEEKS for fluoxetine) before starting a **MAOI** [Monoamine-oxidase inhibitor, none on the Mercy Ships list]. A gap of TWO WEEKS is needed after stopping MAOI before starting another antidepressant.
- **Adverse effects:** diarrhoea, nausea/vomiting, headache, restlessness and anxiety. They tend to cause less sedation, cardiotoxicity and antimuscarinic effects. Caution use in epilepsy as it lowers the convulsion threshold.
- **Hyponatraemia** has been associated with all types of antidepressants (usually in the elderly). Consider in all patients who develop drowsiness, confusion or convulsions during treatment.

#### 4.04 ANTIEPILEPTICS

##### WHO MODEL FORMULARY 2004 NOTES:

Treatment should always be started with a single drug, but the choice of an anticonvulsant can only be made on an individual basis and will depend on the efficacy of the drug and the patient's tolerance of treatment. If a drug fails to control the seizures after it has been used in full therapeutic dosage for an adequate period, or if it is not tolerated, it should be gradually substituted with another with the first drug being withdrawn only when the new regimen is mainly established. If monotherapy is ineffective, two drugs should be given in combination and several regimens may need to be tried before the most appropriate is found.

Initial dose of the drug of choice should be determined on the basis of the degree of urgency, the size and age of the patient. It should be increased gradually until an effective response is obtained. All antiepileptics commonly produce neurological adverse effects at too high a dose, and patients should be monitored closely for adverse effects to help in accurate dose titration. Except for phenytoin, it is rarely useful to measure plasma-drug concentrations as an aid to dose adjustment. Non-compliance because of inappropriate dosing and overdosing is a major impediment to effective antiepileptic treatment. Patients should ideally remain under supervision throughout treatment.

GENERALIZED TONIC-CLONIC, SIMPLE PARTIAL AND COMPLEX PARTIAL SEIZURES. **Carbamazepine** [not on Mercy Ships list], **phenobarbital**, **phenytoin**, and **valproate** [not on Mercy Ships list] are widely used in the treatment of these conditions. However, each of these drugs is associated with dose-related and idiosyncratic adverse effects and monitoring of haematological and hepatic function is often advised, particularly for carbamazepine & valproate.

ABSENCE SEIZURES. Both **ethosuximide** and **valproate** [both not on Mercy Ships list] are widely used in the treatment of absence seizures (petit mal) and are usually well tolerated. However, ethosuximide can, rarely, cause lupus erythematosus and psychoses which call for immediate, but cautious, discontinuation. Absence seizures are commonly associated with tonic-clonic seizures and valproate is preferred since it is effective in both disorders.

TONIC, ATONIC AND ATYPICAL ABSENCE SEIZURES. **Phenobarbital** or **phenytoin** is widely used for tonic seizures, **valproate** [not on Mercy Ships list] for atonic seizures, and **clonazepam** for atypical absence seizures.

MYOCLONIC SEIZURES. **Valproate** [not on Mercy Ships list] is widely used and most effective for juvenile myoclonic seizures. However, both valproate and this type of seizure are associated with a high relapse rate and it is often necessary to continue therapy indefinitely. Other myoclonic seizures are often

resistant to treatment and some do not have an epileptic basis. **Valproate** or **clonazepam** [both not on Mercy Ships list] can be of value in this case and other antiepileptic drugs may be useful in intractable cases. Both drugs are generally well accepted (although tolerance to clonazepam reported).

**INFANTILE SPASM (INFANTILE MYOCLONIC EPILEPSY).** Infantile spasms, which are often associated with severe brain damage, can be resistant to antiepileptic drugs. **Clonazepam** is sometimes of value in resistant cases.

**FEBRILE CONVULSIONS.** Brief febrile convulsions usually respond to sponging with tepid water and by giving an antipyretic such as paracetamol (section 2.1.2). Recurrent febrile convulsions or prolonged convulsions (those lasting 15 minutes or longer) are treated with **diazepam**, either rectally in solution or by intravenous injection, to prevent possible brain damage. *Intermittent prophylaxis*, with diazepam administered at the onset of fever, may prevent recurrence of febrile convulsions, but only in a small proportion of children. Use of antiepileptics for *continuous prophylaxis* is controversial; it is probably indicated in only a small proportion of children including those whose first seizure occurred during the first 14 months of life, or who already have evident neurological abnormalities, or who have had previous prolonged or focal convulsions. **Phenobarbital** may be used for this purpose but careful clinical monitoring and dosage adjustment are necessary in order to minimize the risk of adverse effects. **Valproate** [not on Mercy Ships list], although effective, is not recommended because of greater risk of hepatotoxicity in young children.

**STATUS EPILEPTICUS** is a medical emergency which carries a high mortality rate. Initial management includes positioning the patient to avoid injury, supporting respiration including provision of oxygen, maintaining blood pressure, and the correction of any hypoglycaemia; maintenance of the airway and assisted ventilation are crucial even when the seizures are controlled, because the drugs used in its management may also depress respiration. IV **diazepam** is often effective in status epilepticus. Diazepam acts rapidly and should be administered first and should be followed immediately by a loading dose of **phenytoin** which has a longer-acting effect. When cannulation is impossible, diazepam may be administered rectally as a solution (absorption from suppositories is too slow for treatment of status epilepticus). Intravenous **phenobarbital** is also effective but is more likely to cause respiratory depression; it is used in refractory cases but should be avoided in patients who have recently received oral phenobarbital. Rectal paraldehyde may also be used; it causes little respiratory depression and is therefore useful where facilities for resuscitation are poor. If seizures continue despite treatment, general anaesthesia may be required. The underlying cause must be identified and remedied in all cases.

[Mercy Ships note: Please refer to the WHO Formulary 2004 for the full notes including antiepileptics withdrawal and their use in pregnancy & breastfeeding.]

---



#### 4.05 ANTIMIGRAINE MEDICINES

##### WHO MODEL FORMULARY 2004 NOTES:

Chronic recurrent headache is associated with many disorders, both somatic and psychogenic. An accurate diagnosis must consequently be made before appropriate treatment can be initiated for migraine. Untreated, migraine attacks last for several hours and sometimes for as long as 3 days. Migraine headache is frequently accompanied by episodes of gastrointestinal disturbance including nausea and vomiting. The headache may be preceded or accompanied by aura (classical migraine) which is characterised by visual disturbances such as flickering lines and fragmented vision or sensory disturbances such as tingling or numbness; rarely, hemiparesis or impaired consciousness may occur. Migraine without aura (common migraine) is the more common form occurring in about 75% of patients who experience migraine.

Emotional or physical stress, lack of or excess sleep, missed meals, menstruation, alcohol and specific foods including cheese and chocolate are often identified as precipitating factors; oral contraceptives may increase the frequency of attacks. Avoidance of such precipitating factors can be of great benefit in preventing or reducing the frequency of attacks and should be addressed in detail. Women taking combined oral contraceptives who experience an onset or increase in frequency of headaches should be advised of other contraceptive measures.

The two principal strategies of migraine management are treatment of acute attacks and prophylactic treatment.

**ACUTE MIGRAINE ATTACK.** Treatment of acute attacks may be non-specific using simple analgesics, or specific using an ergot alkaloid such as ergotamine [Not on Mercy Ships List, WHO notes on ergotamine edited from this section]. If nausea and vomiting are features of the attack, an antiemetic drug may be given. Treatment is generally by mouth; some drugs are available as suppositories which may be administered if the oral route is not effective (poor oral bioavailability, or absorption from the gut impaired by vomiting) or not practicable (patient unable to take drugs orally). Simple analgesics including NSAIDs (nonsteroidal anti-inflammatory drugs) can be effective in mild to moderate forms of migraine if taken early in the attack; most migraine headaches respond to **paracetamol**, **acetylsalicylic acid** or an NSAID such as **ibuprofen** (see section 5.01). Peristalsis is often reduced during migraine attacks and, if available, a dispersible or effervescent preparation of the drug is preferred because of enhanced absorption compared with a conventional tablet. The risk of Reye syndrome due to acetylsalicylic acid in children can be avoided by giving paracetamol instead. Frequent and prolonged use of analgesics by migraine sufferers may lead to analgesic-induced headache.

WMF 24.1-24.3, 5, 7  
BNF 4.1-4.3, 4.8, 4.7.4

Central Nervous System

An antiemetic such as **metoclopramide**, given as a single dose orally or by IM injection at the onset of a migraine attack, preferably 10-15 minutes before the analgesic or ergotamine, is useful not only in relieving nausea but also in restoring gastric motility, thus improving absorption of the antimigraine drug.

Products which contain barbiturates or codeine are undesirable, particularly in combination with ergotamine, since they may cause physical dependence and withdrawal headaches.

---

<b>GENERIC (TRADE) NAME</b>	<b>CAT.</b>	<b>INDICATION/DOSE</b>
<b>Propranolol Hydrochloride Tab 40mg (Inderal/Avlocardyl)</b>	EML	Migraine prophylaxis: <i>by mouth</i> Adult 40mg 2-3 times daily, maintenance 80-160mg daily in divided doses.

**COMMENT/CAUTIONS:**

- Consider aspirin or paracetamol for acute attack pain relief.
- Consider metoclopramide for nausea & vomiting.

NOTE. For Antiemetics, see Chapter 01 Gastrointestinal System Section 1.02.

NOTE. For Antihistamines, see Chapter 03 Respiratory System Section 3.03 Antihistamines & Antiallergics.