

**GUIDELINES OF DRUGS COMMONLY USED
IN TREATING MENTAL ILLNESS
AND RELATED DISORDERS**



**Ministry of Health
FIJI**

2010

ACKNOWLEDGEMENTS

These guidelines were assembled by Dr D G Chaplow¹ from publicly available, evidenced-based material, particularly from the ‘WHO PIMHnet Mental Health Information Package’ and other sources.² The ‘guidelines’ were peer-reviewed by Prof Frances Hughes and Dr Charles Hornabrook. The below listed persons assisted during a short-term consultancy funded by the WHO, 2008/9:

Mr. Peter Zinck, (former) Chief Pharmacist, Fiji Pharmaceutical Services
Dr Odille Chang, Medical Superintendent, St. Giles Hospital
Mr. Apolosi Vosanibola
Clinicians of the St. Giles Hospital
Dr Temo Waqanivalu WHO Representative, South Pacific
Ms Muniamma Gounder, Inspectorate & Regulatory Pharmacist
Ms Vinita Prasad, Acting Chief Pharmacist

DISCLAIMER

These are guidelines only. They must be used in the context of adequate service-user/patient assessment, and competent judgment of the clinician/practitioner. Every effort has been made to ensure accuracy and ‘best-practice’ of the information. The authors and sponsors therefore cannot take responsibility for any adverse event consequent upon the use of this document.

¹ Honorary Clinical Associate Professor, University of Auckland; Consultant Psychiatrist, Director of Mental Health and Chief Psychiatrist, Ministry of Health, New Zealand

² Refer to Bibliography

PREFACE

The publication of the *Psychiatry Drug Guidelines* represents the culmination of the efforts of the National Medicines and Therapeutics Committee to publish clinical drug guidelines for common diseases seen in Fiji. These guidelines are targeted for health care settings. It sets the gold standards for the use of psychiatry drugs in Fiji. These guidelines have taken into account the drugs available in the Fiji Essential Medicines Formulary (EMF) in recommending treatment approaches. All recommended drug therapies are either evidence-based or universally accepted standards.

It is hoped that these guidelines will be used by all health care workers in their daily care of patients suffering from psychiatric conditions.

Dr Eloni Tora

Chairman

National Medicines and Therapeutics Committee

2010

CONTENTS

1.0 How to use these guidelines	5
2.0 General comments on prescribing	6
3.0 Medications used in the treatment of mental and related Disorders	8
3.1 Mood Disorders and antidepressants	8
3.2 Anxiety Disorders and Anxiolytics	15
3.3 Psychotic and related Disorders and antipsychotic drugs	19
3.4 Bipolar Disorders and mood stabilising drugs	28
4.0 Management of behavioural and psychiatric emergency	34
5.0 General Information on Psychotropic drugs	38
6.0 References and Bibliography	43

List of tables:

Number	Title	Page
Table 1	Second generation drugs or ‘atypicals’	12
Table 2	Effective drug treatments for depression	12
Table 3	Serotonin States	14
Table 4	Comparative information for Benzodiazepines	17
Table 5	Signs and symptoms of schizophrenia	20
Table 6	Side-effects of Antipsychotic medications	22
Table 7	Usual therapeutic Doses (Depot)	25
Table 8	Usual therapeutic doses (oral)	25
Table 9	Summary of medications used to treat mental illness	38

List of Boxes:

Number	Title	Page
Box 1	Treatment of acute presentations	29
Box 2	General treatment guide for Lithium toxicity	32
Box 3	Special points re tranquillization in psychiatric settings	36

1.0 HOW TO USE THESE GUIDELINES

Clinical Guidelines are ‘living documents’. They have little utility unless useful to the clinicians by being up-to-date, relevant, and readily available.

The objective of these guidelines is to promote ‘best practice’. This cannot occur in isolation and ideally the clinician should be orientated to his/her task by a period of instruction which might include the use of these mental health treatment guidelines as well as peer-review and on-going education.

The guidelines are not exhaustive. They were designed to be useful for the range of clinicians found in the Multi Disciplinary Team (MDT), including primary and secondary clinicians, doctors, nurses, and allied professionals. Thus the material ranges from basic to complex. The focus is on medication used in common mental illnesses and related disorders.

These guidelines don’t replace dedicated formularies, articles, text-books, information for service-users/patients, and/or specialist information. Nor do they replace formal education. They do provide references to sources of information including a small bibliography and relevant references to web-sites.

Note: people who present with mental health problems are referred here as ‘patients’ and ‘service-users’.

2.0 GENERAL COMMENTS ON PRESCRIBING

When prescribing medication:

Don't use psychotropic medication

- Unless you are clear about what you are treating and the causal (or aetiological) factors
- Unless you have balanced the advantages of drug treatment with the risks of side-effects
- Until you either have the patient's permission to proceed or the legal mandate to do so
- Unless you are prepared to carefully follow-up and monitor the results of your prescribing

Note:

Biological causes of mental disorder lead to biological treatments;

Psychological causes of mental disorder lead to psychological treatments;

Social causes of mental disorder, lead to social remedies.

Understanding the cause of the problem (aetiology) will act as a guide to what treatment-intervention is required.

Principles for determining when to use medication

- If possible, identify the type of mental illness. If you know the diagnosis, this will make the treatment-decision much easier
- Depending on the illness, decide whether medications are required
- Use the guidelines outlined in the section below to determine the specific medication required and refer to websites such as Medsafe (www.medsafe.govt.nz)
- Explain the use of the medication clearly to the patient – the purpose of the medication, how to take it and for how long
- To limit side effects, some medications need to be started incrementally and increased in small steps until the required dosage is required. Detail about side effects is provided further on in this section
- Always ensure that the patient is monitored for side-effects
- Never exceed the maximum recommended dose

- Avoid using some drugs for too short a period (such as antidepressants) or for too long (such as sleeping pills)
- Resist the temptation to continue medications as before in follow up clinics. i.e., if you see someone who has taken a medication for years, do not assume that this is appropriate – review their health status
- Be aware of the common trade name and costs of medications in your area.

Adapted from Patel 2003

Generally speaking, the following mental illnesses benefit from medication

- Severe mental disorders such as schizophrenia, manic-depressive illnesses and acute psychoses
- Mental disorders, particularly those that have lasted more than a month and are seriously affecting the person's day to day life (for example depression, prolonged grief or some personality disorders)
- When the person is experiencing acute stress such as following the death of a close relative.
- When advice, counseling and social supports have failed to resolve the mental problem.

Types of medications to use

When you have made the decision to use medication, you then need to determine which one to use. There are four major groups of medication corresponding to the four main groups of mental illness:

1. antidepressants used to treat depression
2. anti-anxiety medications such as Diazepam and Beta-Blockers to treat anxiety related disorders (short-term only) and some other conditions (muscle relaxation, status epilepsy)
3. antipsychotic medications for severe mental disorders (e.g. schizophrenia, bipolar DO)
4. drugs to stabilize manic-depressive illness and potentiate other medication.
5. and, treatment of other conditions

Additionally, there is medication to help control some of the side-effects of some medications. Patient education is also required.

3.0 MEDICATIONS USED IN TREATMENT OF MENTAL AND RELATED DISORDERS

3.1 Mood Disorders: Antidepressants

Listed in the Fiji Essential Drug List

Amitriptyline, tabs 25mgs, Imiprimine, tabs 25mgs, Doxepin caps 25mgs, and Fluoxetine HCL, tabs 20mgs

i) Mode of action:

Thought to be determined by receptor-mediated signal transduction in serotonergic or noradrenergic pathways.

ii) Clinical indications

In addition to use in depression, the ‘anti-depression’ medications are also useful in the treatment of generalised anxiety disorder, panic disorder, obsessive compulsive disorder, agoraphobia, social phobia (social anxiety disorder) and bulimia nervosa, in addition to other indications such as chronic pain.

Note: Combinations of antidepressants have not been shown to be more effective than monotherapy in first-line treatment. There is little evidence supporting the use of combined antidepressants in ‘treatment-resistant’ depression and there are significant concerns at the potential for serious drug interactions.

Tricyclic Antidepressants (TCA’s) (Amitriptyline, Imiprimine and Doxepin)

i) General:

Tricyclic antidepressants (TCAs) are nonselective reuptake inhibitors of noradrenaline and serotonin. They are absorbed rapidly after oral administration and they are extensively metabolised in the liver. The major metabolites of some are active compounds. Individual dosage adjustment is required to achieve optimum therapeutic effects, as there are marked individual variations in steady-state plasma concentrations at the same dosage.

ii) Use in children:

They should not be used in children under the age of 16 years

iii) Use in the elderly:

Older persons are more susceptible to adverse effects, including delirium, so observe special caution.

iv) Use in pregnancy:

There is no evidence that exposure to tricyclic antidepressants (TCAs), even in the first trimester, carries any significantly increased risk of malformation. These antidepressants are often considered the drugs of choice in severe depression during pregnancy. Isolated case reports have suggested a possible increased risk with the use of Doxepin, but this evidence is inconclusive. Doses may need to be increased in late pregnancy to maintain efficacy.

iv) Side effects and (drug) interactions:

Common adverse effects include dry mouth, blurred vision, constipation, urinary retention, orthostatic hypotension, sexual dysfunction, weight gain and sedation. Sedation may persist the following day after night-time dosing and the effects of alcohol and benzodiazepines may be potentiated. Patients should be warned that this may affect their ability to drive and operate machinery safely.

In patients with pre-existing cardiac conduction defects, TCAs may cause impairment of cardiac conduction and may prolong the QTc interval. Avoid concurrent use with other drugs that can prolong QTc interval. Cardiac toxicity is the main cause of the high lethality of TCA overdose and such patients should have cardiac monitoring.

TCAs can lower the seizure threshold and should be used with caution in patients with epilepsy.

The more serotonergic TCAs, (e.g. amitriptyline and imipramine) should not be co-administered with other serotonergic drugs as likelihood of serotonin toxicity can be increased. Individual TCAs are metabolised by differing hepatic isoenzymes hence their potential for interactions varies.

v) Clinical notes of caution when using TCA's

Note: some people are unable to tolerate their adverse effects and sedating properties. They are also potentially lethal in overdose.

Note: Surveys of TCA-use consistently show inadequate dosage in 50% of patients treated for major depression. Serum concentrations of some TCAs (such as nortriptyline and imipramine) may be helpful in determining the appropriate therapeutic dosage. Note the ‘therapeutic window’.

Note: In all TCAs, lower doses are likely to be required if the patient has reduced ability to metabolise medication (such as impaired hepatic functioning) or increased vulnerability to adverse effects.

Note: Use TCAs with extreme caution in the presence of cardiac disease

vi) Dose ranges:

Tricyclic antidepressants: (Amitriptyline, Doxepin, Imipramine)

A TCA 50 to 75 mg orally, at night, increasing every 2 to 3 days (depending on adverse effects) to 150 mg at night by the 7th day. If there is no response after 3 to 4 weeks, dosage may be increased at 3 to 4 week intervals by increments of 25 to 50 mg per day (while monitoring the patient for adverse effects) to 200 to 250 mg at night.

Note:

- **Some people are unable to tolerate their adverse effects and sedating properties**
- **TCAs are potentially lethal in overdose**
- **TCAs should not be combined with other antidepressants. Significant unpredictable drug interactions may occur, particularly with the SSRIs and interactions with MAOIs may be fatal**

Selected Serotonin Reuptake Inhibitors (SSRIs) (Fluoxetine)

i) General

These drugs selectively inhibit serotonin reuptake. Fluoxetine has a longer half life than other SSRIs and active metabolites which means tapering of the drug when stopping it is usually not required.

SSRIs are metabolised in the liver by cytochrome P450 isoenzymes and can inhibit the metabolism of many other drugs, causing increased plasma drug concentrations and possible toxicity.

ii) Use in children

Apart from Paroxetine, drug trials have not been conducted in children (because of ethical issues) and regulatory authorities in the US and NZ advise extreme caution in their use.

iii) Use in the elderly

Generally safer than TCAs. However, studies raise concerns about a reduction of bone mineral density (BMD) in patients taking SSRIs, which could put them at increased risk of sustaining fractures.

iv) Use in pregnancy:

There are six areas of concern: teratogenicity, spontaneous abortion and premature labour, low birth weight/small-for-dates, poor neonatal adaptation, persistent pulmonary hypertension in the neonate, and neurodevelopmental difficulties in older children. Currently there is no clear evidence to recommend one SSRI over another. However, some potential problems have been reported with use of Paroxetine and Fluoxetine

iv) Side-effects and (drug) interactions

Common adverse effects of SSRIs include nausea, anxiety, diarrhoea, constipation, headache and insomnia. In some patients, a marked stimulation may occur with restlessness and agitation (known as 'akathisia'). Serotonin toxicity can also occur, particularly with high doses or if other serotonergic drugs are co-administered.

SSRIs should not be given with either reversible selective or irreversible nonselective monoamine oxidase inhibitors (MAOIs). These combinations can produce serotonin toxicity, which has been associated with fatalities.

Sexual dysfunction, including loss of libido, anorgasmia and ejaculatory disturbance, commonly occur and may require consideration of different treatment. The use of "drug holidays" or delayed dosing to avoid these effects can lead to relapse of depression or antidepressant discontinuation symptoms. The syndrome of inappropriate antidiuretic hormone (SIADH) may occur and is more common in the older person. As hyponatraemia can be asymptomatic, consider checking the base-line serum sodium level in older people. This should then be repeated within a month, or earlier if the patient has symptoms

SSRIs can interfere with haemostasis, due to action on serotonin release from platelets, and may increase the risk of bleeding. Risk of upper gastrointestinal (GI) tract bleeding in patients taking SSRIs is significantly increased when an SSRI is combined with a nonsteroidal anti-inflammatory drug or low-dose aspirin. Patients vulnerable to GI bleeding (e.g. those with a history of peptic ulcer disease, oesophageal varices or undergoing surgery) should be observed carefully and considered for an alternative class of antidepressant, or given a protective drug.

SSRIs do not interact with alcohol and have minimal effects on psychomotor function. They are relatively free of cardiovascular adverse effects and have low lethality in overdose.

In adults over the age of 25, a proposed connection between SSRI use and increased suicidal ideation and behaviour is not supported by evidence, even though SSRI-induced agitation may temporarily enhance suicidal ideation/behaviour soon after initiation of treatment. However, there is evidence of an increased risk of suicidal ideation in children and adolescents taking SSRIs.

v) Dose ranges

Table 1: ‘second-generation drugs’ or ‘atypicals’

Drug	Usual initial treatment dose, per day [NB1]	Maximum daily dose [NB2]
Citalopram	20 mg, in the morning	60 mg
Escitalopram	10 mg, in the morning	20 mg
Fluoxetine	20 mg, in the morning	40 to 80 mg
Fluvoxamine	Starting dose 50 mg in the evening. Generally increase to 100 mg in 5 to 7 days as tolerated	300 mg [NB3]
Mirtazapine	15 to 30 mg, in the evening	60 mg (increase dose by increments of 15 to 30 mg)
Moclobemide	300 or more commonly 450 mg, daily after food	600 mg in 2 divided doses or a single dose (increase dose by increments of 150 mg)
Paroxetine	20 mg, in the morning	50 mg (increase by increments of 10 mg)
Reboxetine	4 to 8 mg, in 2 divided doses	10 mg (increase by 2 mg)
Sertraline	50 mg, in the morning	200 mg
Venlafaxine	75 mg, in the morning	300 mg

NB1: This dose is effective for most patients and is the usual starting dose.

NB2: Dose may be increased at 3 to 4 week intervals.

NB3: Doses of Fluvoxamine above 150 mg daily may be given in 2 divided doses for better tolerability.

Note: when SSRI's are used in anxiety DOs, higher doses are often indicated

Table 2: Effective drug treatments for depression

Treatment	Does it work?	Considerations	Risks
Serotonin Selective Reuptake Inhibitor (SSRI) anti-depressant medication (e.g. Fluoxetine, Paroxetine, Citalopram, etc)	Yes	Some people feel agitated on SSRIs and the doctor should be advised if this occurring.	Concerns that they may prompt suicidal feelings in some mean close monitoring in initial stages.
Tricyclic Anti-depressants (TCAs) (e.g. imipramine, nortriptyline, etc)	Yes	These are more likely to be used if the depression is severe and/or another treatment has not worked sufficiently	Side effects are more common than SSRIs, especially early in treatment. Not suitable when some medical conditions are present. Dangerous in overdose.
Venlafaxine – this is a Serotonin and Noradrenaline Reuptake Inhibitor (SNRI) anti-depressant	Yes	Particularly useful when other treatments have been unsuccessful or for severe depression	Side effects similar to TCAs above

Note: Assessment of depression should include full evaluation and formulation, including:

- risk assessment
- subtype, severity and duration of depression;
- comorbidity (with medical and/or psychiatric illness or substances);
- current stresses, strengths and supports;
- relevant personal and family history, and
- past history of any mental illness

Serotonin States:

Distinguishing between clinical features of an SSRI discontinuation syndrome, adverse effects of SSRIs, depression symptoms (or exacerbation) and serotonin toxicity (Table 3)

Table 3: Serotonin States: Note that there may be overlap between these conditions and the differentiation may be clinically difficult.

	Withdrawal syndrome	Side effects	Depression	Serotonin toxicity
Clinical features	dizziness, nausea, anxiety, headache (most commonly reported symptoms)	asthenia, diarrhoea, nausea, anxiety, dizziness, insomnia, nervousness, tremor, somnolence (most common symptoms)	depression and lack of interest predominate, but can have prominent anxiety and sleep disorder	Abdominal cramps, agitation, diarrhoea, myoclonus, tremulousness, coma, tachycardia, hypotension or hypertension, confusion, disorientation, profuse sweating, hyperpyrexia. <i>If severe, refer immediately to an emergency department.</i>
Context	rapid reduction or stopping of SSRIs check if patient has altered dose, forgotten tablets, or run out of tablets	mostly in the first 1 to 2 weeks of treatment mostly settle if medication is continued check not a drug interaction, especially SSRI + TCA; stop concurrent TCA	continuation or worsening of initial illness about 10% to 20% of patients relapse with continued treatment; some improve with an increased dose, others need change of medication	overdosage drug interaction, especially SSRI + MAOI or SSRI + serotonergic TCA (e.g. Clomipramine, amitriptyline, imipramine) inadequate drug-free interval in changing medications idiosyncratic reaction
Response to increased SSRI dose	usually relieved	usually worsens	no acute change, except possible adverse event	worsens, could be dangerous
Response to decreased SSRI dose	usually worsens	usually relieved	no acute change, or subsequent worsening with relapse, or discontinuation syndrome	usually relieved if SSRI (and interacting medication if possible) ceased
Symptoms persist despite intervention	seek a psychiatric second opinion	seek a psychiatric second opinion	seek a psychiatric second opinion	<i>emergency; urgent referral to an emergency department is necessary</i>

Adapted from: Tiller JWG. Medicinal mishaps. Aust Prescr 1998;21:63.
<http://www.australianprescriber.com/magazine/20/3/artid/261>

3.2 Anxiety Disorders: Anxiolytics

Listed in the Fiji Essential Drug List

Diazepam (Tab 5mg, Inj. 10mg/2mls), Propranolol (Inj. 1mg/1ml, Tab 10mg, Tab 40mg)
(NB: Propranolol is a B-blocker used in anxiety-disorders)

Diazepam

i) Mode of action:

Benzodiazepines act by potentiating the action of gamma-aminobutyric acid (GABA) at the GABA_A receptor resulting in neuronal inhibition. Benzodiazepines are generally rapidly absorbed after oral ingestion. They are metabolised both by oxidation, which may produce active metabolites. Most differences between benzodiazepines are explicable in terms of different pharmacokinetic properties.

ii) Clinical indications

Benzodiazepines are effective in relieving anxiety symptoms and can induce sleep. They are also used for their antiepileptic actions, including the reduction of myoclonus, and for their skeletal muscle relaxant and amnesic effects. Their main disadvantage is physical dependence and they can impair performance and affect judgment, so driving and other skilled tasks can be affected.

Note: There is little basis for the use of more than one benzodiazepine concurrently in any patient.

iii) General:

- Anxiety disorders are generally separated into a number of discrete conditions (as described in DSM-IV). However, there is significant co-morbidity between the different anxiety disorders, and with mood disorders and substance use or dependence.
- Anxiety symptoms may be very prominent in depressive disorders. Lack of response to antianxiety therapy may reflect an underlying depressive illness requiring antidepressant treatment.
- For many anxiety disorders, psychological therapies such as cognitive behavioural therapy (CBT) are the most appropriate initial choice.

Subsets of anxiety disorder

- Adjustment disorder with anxious mood
- Generalised anxiety disorder
- Panic attack
- Panic disorder
- Obsessive compulsive disorder (OCD)
- Phobic disorders (Simple phobias, Social Phobias, Agoraphobia)

Note: The primary treatments for anxiety disorders are nonpharmacological, including counselling, relaxation, problem-solving, stress management, and cognitive behavioural therapy (CBT)

iv) Use in children:

Caution should be exercised

v) Use in the elderly:

Older persons are particularly vulnerable to the adverse effects of ataxia (with consequent falls and injury), confusion. Therefore, use with caution.

vi) Use in pregnancy:

The issue of whether first trimester exposure to benzodiazepines is associated with increased risk of cleft lip and/or palate remains controversial. After the first trimester, anxious patients who do not respond to counselling or sleep hygiene measures may benefit from the intermittent use of low-dose benzodiazepines as hypnotics. If benzodiazepines (especially those with long half-life) are taken in late pregnancy, they can cause neonatal drowsiness, respiratory depression, poor temperature regulation, poor feeding and hypotonicity (the 'floppy infant' syndrome). Neonatal withdrawal symptoms have also been reported.

vi) Side effects and (drug) interactions:

Important points to remember when using this group of medication include:

- patients need to avoid using alcohol
- they should not be taken by women in the last stages of pregnancy
- do not give them for more than four weeks as they can cause dependence problems.
- Some benzodiazepine medicines have a value on the illicit drug market (e.g. *Diazepam*)

vii) Clinical notes of caution when using

Note: its main disadvantage is physical dependence and it can impair performance and affect judgment, so driving and other skilled tasks can be affected.

Note: There is little basis for the use of more than one benzodiazepine concurrently in any patient.

Note: in general do not give diazepam by intramuscular injection, as absorption is poor and erratic.

Note: in regard to side-effect profile, older persons are particularly vulnerable to the adverse effects of ataxia (with consequent falls and injury), confusion, memory loss and cognitive impairment. The potential for the development of tolerance, dependence and a withdrawal syndrome are important considerations.

Note: dependence develops rarely in patients taking normal therapeutic doses of these drugs for short periods (e.g. 1 to 2-weeks). However, about a third of patients on long-term treatment may have difficulty in reducing or stopping benzodiazepines.

Other Benzodiazepines have shorter half-lives and although they have greater risk of dependence, are useful in sleep disorders and rapid sedation. Examples include Clonazepam and Lorazepam.

vii) Dose ranges:

Table 4: Comparative information for benzodiazepines, Zolpidem and Zopiclone

Drug	Approximate equivalent dose [NB1] (mg) to diazepam 5 mg	Length of action [NB2]
Alprazolam	0.5	short acting
Bromazepam	3	medium acting
Clobazam	10	long acting
Clonazepam	0.25	long acting
Diazepam	5	long acting
Flunitrazepam	1	long acting
Lorazepam	1 [NB3]	medium acting
Midazolam	acute use only	very short acting
Nitrazepam	2.5	long acting
Oxazepam	15	short acting
Temazepam	10	short acting
Triazolam	0.25	very short acting
Zolpidem	–	very short acting

Zopiclone

–

very short acting

NB1: the widely varying half-lives and receptor binding characteristics of these drugs make exact dose equivalents difficult to establish

NB2: very short acting (half-life <6-hours); short acting (half-life 6–12-hours); medium acting (half-life 12–24-hours); long acting (half-life >24-hours). Note that even very short acting and short acting benzodiazepines can have a long half-life in some patients

NB3: Lorazepam may be relatively more potent at higher doses

Propranolol

i) Mode of action:

Propranolol is a nonselective beta-blocker that is used to treat the motor effects of antipsychotic-induced akathisia and prominent sympathetic symptoms of social phobia (social anxiety disorder).

ii) Clinical indications

Social anxiety in adults. For non-generalised social anxiety disorder (including performance anxiety) the goal of pharmacological treatment is to reduce the specific physiological symptoms (manifestations of sympathetic overactivity) of tremor, palpitations, sweating, which are distressing or unpleasant during a particular task.

iii) General:

Beta blockers should be avoided in patients with asthma or severe peripheral vascular disease. Adverse effects include precipitation of bronchospasm, lethargy, depression, aggravation of Raynaud's phenomenon, intermittent claudication, heart failure, depressed exercise tolerance and occasional CNS symptoms.

iv) Use in children:

Apply caution unless there are strong indications

v) Use in the elderly:

Caution should be exercised due to postural hypotension

vi) Side effects and (drug) interactions:

See above

vii) Clinical notes of caution when using

See above

vii) Dose ranges:

Propranolol 10 to 40 mg orally, 30 to 60-minutes before the social event or performance.

3.3 Psychotic Disorders (Schizophrenia and related disorders): Antipsychotics

i) Listed in the Fiji Essential Drug List

Chlorpromazine (Tabs 50mgs, Tabs 100mgs, Inj 50mg/2mls);
Droperidol, (Inj 10mg/2mls), Flupenthixol (Inj 100mg/1ml),
Fluphenazine Decoanate, (Inj 25mgs/1ml),
Haloperidol (Tab 1.5mg, Tab 5mg, Inj 5mg/1ml) Olanzapine (Tab 10mg)
Thioridazine (Tabs 10mg, 50mg, 100mg **note**: now out of production)
Trifluoperazine HCL (Tabs 1mg, 5mg)

Note: There are two groups of antipsychotic medications:

1. 'Typical' (or 'first generation') antipsychotics including *Chlorpromazine, Haloperidol, Trifluoperazine, Fluphenazine and Droperidol.*
2. 'Atypical' (or 'second generation') antipsychotics including *Olanzapine, Clozapine and Risperidone.* (The last two are not in the Essential Medicines Formulary but are often seen in repatriated patients)

Generally the older drugs produce more discomforting side effects (e.g. Extra Pyramidal Side-effects or EPS) and are less effective in treating negative symptoms) but are cheaper and often more readily available than the newer antipsychotic drugs.

Further notes:

-first-generation antipsychotics have been associated with a range of disabling adverse effects (known as EPS) such as acute dystonia, akathisia, parkinsonism, tardive dyskinesia and neuroleptic malignant syndrome. These adverse effects are less frequent with the second-generation antipsychotics when used at the recommended doses.

-neuroleptic malignant syndrome is a rare but potentially fatal adverse effect that requires emergency management (see below)

- most have metabolic side effects, especially the second generation drugs (see below). These side-effects include weight gain, increased salivation, and induced diabetes.

-excessive weight gain is common with Olanzapine use and can precipitate type 2 diabetes.

i) Mode of action:

Although the exact mechanism of action of antipsychotics is unknown, all available antipsychotics, except aripiprazole, competitively block dopamine D₂ receptors. Second-generation antipsychotics, except amisulpride and aripiprazole, are distinguished as a class by greater serotonin 5-HT₂ versus dopamine D₂ blockade. Aripiprazole is a partial agonist at dopamine D₂ receptors. Hence it should decrease excessive levels and increase low levels of dopamine, avoiding both overactivity and underactivity.

Most antipsychotic drugs are absorbed rapidly from the gut and are highly lipid soluble. There is widespread interpatient variability in the pharmacokinetics of and responses to these drugs.

ii) Clinical indications

Schizophrenia and related psychoses.

Table 5: **Signs and symptoms of schizophrenia**

Positive	Negative	Cognitive
hallucinations (e.g. hearing voices)	lack of motivation	impaired planning
delusions (e.g. persecutory, bizarre, grandiose)	poor self-care	reduced mental flexibility
disorganised thinking, speech and behaviour	blunted affect	impaired memory
	reduced speech output	impaired insight
	social withdrawal	

Related Psychotic Disorders

- **Brief psychotic disorder** is an illness of less than two weeks' duration in which positive psychotic symptoms (hallucinations, delusion and thought disorder) predominate.
- **Schizophreniform disorder** denotes a psychotic illness with many of the features of schizophrenia, but with a shorter duration of symptoms (less than 6-months).

- **Delusional disorder (paranoid disorder)** usually presents in middle or late adult life. It is characterised by delusions (e.g. grandiose, persecutory, erotomanic or somatic). Patients have less general impairment than those with schizophrenia; however, they may have isolated areas of dysfunction related to their delusional ideas. Treatment with medication is the same as for schizophrenia.
- **Schizoaffective disorder** has prominent mood symptoms in addition to the core symptoms of schizophrenia. Patients may have episodes of elevated mood, and/or episodes of depression. Management usually involves the combination of antipsychotic with antidepressants (when depressed) and/or mood stabilisers (when manic, or for prophylaxis)

iii) General:

Medication is essential for effective treatment of schizophrenia for most people. However, it works best when integrated with good quality psychosocial treatment.

First generation anti-psychotics: *Chlorpromazine, Haloperidol, Trifluoperazine*

Second generation anti-psychotics: *Olanzapine, Risperidone, Clozapine, Quetiapine.*

The first-generation medications are effective; however they often have more upsetting side effects if used in high doses.

The second-generation medications are not problem-free with the development of metabolic syndrome, in some, being a particular problem.

The positive/active symptoms of psychosis, such as hallucinations and delusions have been the main focus of medication treatment. Newer anti-psychotic medication may also be helpful in treating the negative symptoms such as those associated with mood, thinking and socialising. Feelings of anxiety and agitation are also helped by anti-psychotic medication.

Depot (injected) medication is a form of anti-psychotic medication which slowly releases the drug over one to four weeks (depending on the drug). Some people prefer the depot medication as they find remembering to take pills every day difficult. Depot medications can cause the same side effects as oral medications.

Other medication may be prescribed along with anti-psychotic medication to treat the symptoms of schizophrenia or other symptoms the person might have. There are many medications that are used in conjunction with anti-psychotic medication including:

- Anti-anxiety agents used to treat distress or agitation
- Mood-stabilising agents to treat mood symptoms when they occur in psychosis (Lithium Carbonate, Carbamazepine (Tegretol), and Sodium Valproate)
- Sleeping tablets (hypnotics) to counter insomnia
- Side effect medication (anti-cholinergics, or anti-parkinsonian drugs) used to reduce movement disorders
- Anti-depressants used to treat depression.

Some people will require anti-psychotic medication for long periods. Usually the medication is continued for one to two years after the person has achieved a good recovery from their first episode and is stable in life with regard to relationships, work or accommodation.

iv) Use in children:

May be appropriate given symptomatology and diagnosis. However use with care.

v) Use in the elderly:

Need to watch for orthostatic hypotension. Use medication in incremental doses.

vi) Use in pregnancy:

‘First generation’ antipsychotics: these drugs appear to present no major risk at usual doses.

‘Second generation’ antipsychotics: The safety of the second-generation antipsychotics has yet to be established and there are no consistent reports of deleterious effects on the foetus. Olanzapine has been linked to an increased risk of maternal gestational diabetes, with associated risk to the foetus.

vi) Side-effects and (drug) interactions:

Some people may experience side effects from some medications. However, it is important to first be sure that the person’s complaints are actually side-effects. For example, if a person has felt tired since taking the medication, it may transpire that the person has experienced the symptom since before they began taking medication. Once

you are sure that the person is experiencing side effects there are several things that need to be considered:

- How severe are the side effects? Most medicines produce some side effects and most of the time these are mild and temporary. Ask the person how much distress the side effect is causing. Often the side effect can be tolerated if the benefit of the medication will be evident in a short time
- Can the dose be reduced? Sometimes a small reduction will reduce side effects without affecting the illness or changing the time for taking the medicine
- Can the person take a different medication? Many types of medication can be used to treat the same mental illness. If the side effects are intolerable, try switching to another
- Is the medicine necessary? In some people the need for medicine might be less evident on follow up. The medicine could be stopped and the person seen again in a week to ensure they are still feeling better.

Table 6 – Side effects of anti-psychotic medications

Medication	Side effects	Treatment for side effects
Older typical anti-psychotics – <i>Chlorpromazine,</i> <i>Haloperidol,</i> <i>Trifluoperazine</i>	<ul style="list-style-type: none"> • Movement disorders: Dystonia (muscle spasm) Parkinsonism (tremor, slow movements) Akathisia (restlessness) • Tardive Dyskinesia: Uncontrollable muscle spasms resulting in twisting of body or neck. Occurs in 5% of people taking medication. • Sedation • Galactorrhea (stimulation of milk secretions) • Sexual dysfunction in males • Liver disorder (rare) 	Anti-cholinergic medication (such as Benztropine – Cogentin) Reviewing diet and exercise habits

Newer atypical anti- psychotics (<i>Olanzapine</i> , Risperidone, Clozapine, Quetiapine)	<ul style="list-style-type: none"> • Weight gain • Loss of libido • Hormonal side effects • Sedation • Galactorrhea (stimulation of milk secretions) • Sexual dysfunction in males • Liver disorder (rare) • Constipation 	See section on metabolic syndrome
Clozapine	<ul style="list-style-type: none"> • Agranulocytosis (loss of production of white blood cells which are involved in defending the body from infection leading to an increased chance of experiencing life-threatening infections) – less than 1% chance • Seizures • Sedation • Drooling • Increased heart rate 	<p>An assessment of the white cell level is conducted weekly to prevent the mortality risk.</p> <p>A temperature increase needs immediate investigation. Protocols must be adhered to before this drug can be prescribed. The prescribing clinician needs to refer to international protocols (Ministries or Departments of Health drug safety areas in countries). Check www.medsafe.govt.nz for further information.</p>
Risperidone (low doses few side effects)	<ul style="list-style-type: none"> • Movement disorder • Gastric distress • Mild sedation 	
<i>Olanzapine</i>	<ul style="list-style-type: none"> • Sexual dysfunction • Weight gain • Mild liver dysfunction • Constipation 	
Quetiapine	<ul style="list-style-type: none"> • Drowsiness • Dizziness 	

Adapted from Patel 2003

vii) Notes of caution when using Antipsychotics and treating side-effects

The guiding principle for definitive pharmacological treatment of schizophrenia is to start with a low dose and titrate upwards at a rate and to a level that is optimal for the patient. The opposite applies in the treatment of behavioural emergencies, namely start with a high dose and then titrate downwards.

Patients with a first psychotic episode tend to be very sensitive to antipsychotic drugs and may respond to lower-than-usual doses of antipsychotic drugs.

It is essential to monitor closely for adverse effects of antipsychotic drugs, such as:

- movement disorders (e.g. extrapyramidal adverse effects or akathisia)
- rapid weight gain
- undue sedation
- hyperprolactinaemia causing breast enlargement, galactorrhoea
- sexual dysfunction (this does not appear immediately).

If extrapyramidal adverse effects (dystonia, stiffness, shaking, restlessness) are marked and cannot be avoided by dose adjustment or a change of drug add
Benztropine 1 to 2 mg orally, twice daily or Benztropine 1 to 2 mg IM or IV as a single dose for acute dystonia (see below).

Note: Metabolic effects and ‘Metabolic Syndrome’

Schizophrenia itself is an independent risk factor for diabetes and most antipsychotic drugs increase this risk. In particular, Clozapine and Olanzapine are associated with abnormal glucose tolerance and increased serum lipids. Amisulpride, Aripiprazole and Ziprasidone have less effect on metabolic parameters.

These effects, which may occur in the absence of weight gain, place patients at increased risk of diabetes and cardiovascular disease, risks that are augmented by obesity and lifestyle factors such as smoking and lack of exercise. Fasting blood glucose, serum lipid measurements, waist circumference, weight and blood pressure should be measured around the onset of treatment in all cases and annually thereafter, but at least every six months in patients on Clozapine and Olanzapine. If abnormalities are detected, further investigations should be undertaken, appropriate treatment initiated as indicated, and consideration given to changing to an alternative antipsychotic drug.

All patients should be provided with dietary advice and lifestyle assessment (i.e. patterns of eating, smoking and exercise) and an assertive but supportive therapeutic program aimed at better physical health, with special attention to smoking cessation/reduction, exercise and a balanced diet. Community rehabilitation and support programs can be of value.

Last, it is important to monitor bowel function. Constipation is a major and occasionally lethal side-effect of newer antipsychotic medication.

Note: Neuroleptic (antipsychotic) malignant syndrome

- Neuroleptic malignant syndrome is a potentially lethal adverse effect from treatment with a drug that affects dopaminergic transmission. Antipsychotic drugs are a leading cause of this syndrome which is characterised by severe muscle rigidity, increased temperature, autonomic instability, delirium and raised creatine kinase.
- Treatment depends on the severity of the symptoms. In all cases, discontinue the antipsychotic drug, monitor vital signs and ensure adequate hydration using intravenous fluids. Cool the patient and give deep venous thrombosis prophylaxis. For mild cases conservative management may be sufficient; however, sometimes oral bromocriptine is indicated.
- In a life-threatening situation, treatment in an intensive care unit is indicated. Use:
 - *Bromocriptine 2.5 mg orally, twice daily initially, gradually increasing to 5 mg 3-times a day*
 - *PLUS*
 - *Dantrolene 1 mg/kg/day IV given as a divided dose, every 12 hours increasing up to 10 mg/kg/day.*
- In patients with suspected or documented neuroleptic malignant syndrome, the continuing need for antipsychotics should be reviewed by a psychiatrist. Thirty per cent of these patients develop the syndrome again on re-challenge.
- For those patients who cannot be managed off drugs, the following steps are recommended:
 - wait at least five days before the antipsychotic challenge
 - use an alternative antipsychotic
 - commence on low doses and increase slowly, monitoring closely for signs of re-emergence of the syndrome.

vii) Dose ranges:

Table 7 – Usual therapeutic doses and intensity of common side effects of long-acting (Depot) traditional/’first-generation’ anti-psychotics

Drug	IM Dose Range (mg)³	Dosing interval (weeks)	Sedation	Postural Hypo-tension	Anti-cholinerg ic	Extrapyra-midal	Weight Gain
Flupenthixol Decanoate	12.5-50	2 – 4	+	+	++	+++	+
Fluphenazine Decanoate	20 – 40	2 – 4	++	+	+	+++	+
Haloperidol Decanoate	50 – 200	4	+	+	+	+++	+
Zuclopenthixol Decanoate	200 – 400 ⁴	2 – 4	+++	+	++	+++	+

Table 8 – Usual therapeutic doses and intensity of common side effects of anti-psychotic medications – oral route

Drug	Oral dose range (mg)	Sedation	Postural Hypo-tension	Anti-cholinergic	Extrapyra-midal	Weight gain
Clozapine	100 - 600	+++	+++	+++	+ ¹	+++
<i>Olanzapine</i>	5 – 20	++	+	+	+ ¹	++
Quetiapine	300 – 700	+	++	+	+ ¹	++
Risperidone	0.5 – 6.0	+	++ (initially)	0	+ ¹	+
<i>Chlorpromazine</i>	50 – 600	+++	+++	++	++	++
Droperidol	5 – 10 (IM)	++	+	+	++	+
<i>Fluphenazine</i>	5 – 20	++	+	+	+++	+
<i>Haloperidol</i>	0.5 – 12	+	+	+	+++	+
<i>Haloperidol Decoanate (IM)</i>	25-50/2-4 weeks	+	+	+	+++	+
Pericyazine	25 – 75	+++	++	+++	++	+
Pimozide	2 – 12	++	+	+	++	+
Thioridazine	50 – 600	+++	+++	+++	++	++
Thiothixene	10 – 40	+	+	+	+++	+
Trifluoperazine	10 – 50	++	+	+	+++	+
Zuclopenthixol	50 – 150 ²	+++	+	++	+++	+
Zuclopenthixol dihydrochloride	10 – 75	+++	+	++	+++	+

Key

0=Negligible or absent

+ =Mild

++=Moderate

+++ =Marked

IM=Intramuscular

¹Rarely a problem at usual therapeutic doses

²Single dose not to be repeated for two or three days

³An initial test dose is recommended for all long acting agents especially if the person with schizophrenia has not been exposed to the type of anti-psychotic agent previously

⁴Patients switched from Zuclopenthixol acetate do not require a test dose of Zuclopenthixol Decanoate

Notes on specific antipsychotic and related Drugs:

Clozapine:

- There is strong evidence demonstrating the efficacy of Clozapine for treatment-resistant schizophrenia;
- At least a third of treatment-resistant patients show at least moderate improvement after a 6- to 12-month trial of Clozapine;

- Clozapine requires strict monitoring in light of its potential to cause neutropenia, agranulocytosis, myocarditis, toxic megacolon and cardiomyopathy. Other significant adverse effects include marked sedation, weight gain, dyslipidaemia and hyperglycaemia, lowered seizure threshold, hypersalivation, asthenia, sedation and severe constipation.
- Note: The most common cause of death in those treated with Clozapine is toxic-megacolon (following chronic constipation). Therefore, strict monitoring of bowel function is essential
- Recommended use: Clozapine 12.5 mg orally, twice daily initially, increasing as tolerated and according to patient response. Usual effective daily dose is 200 to 600 mg. The maximum dose is 900 mg daily, but this is not usually required.
- Protocols must be adhered to (see manufacturers recommendations)

Droperidol

Droperidol is only available in parenteral form (i.e. IM/IV). It is more sedating than haloperidol and less likely to cause extrapyramidal adverse effects. Droperidol has a faster onset of action and a shorter duration of action than intramuscular haloperidol. It is used in the emergency control of the acutely disturbed patient and as an adjunct in anaesthesia. Doses greater than 5 mg should not be given without immediate access to ECG monitoring and resuscitation facilities because Droperidol can cause prolongation of the QTc interval.

Depot medications

(Flupenthixol Inj 100mg/1ml, Fluphenazine Decanoate, Inj 25mgs/1ml, Haloperidol, Inj 5mg/1ml)

- The use of long-acting depot preparations of antipsychotic drugs is an option when compliance with oral medication is questionable
- It may take 2 to 4-months to achieve steady-state plasma concentrations for all these drugs; so careful dose adjustment is required.

Anti-cholinergics/Anti-parkinsonian drugs

- **Benzotropine** and **Benzhexol** are antiparkinsonian drugs. They inhibit the action of acetylcholine both peripherally and centrally. The presumed basis for their use as antiparkinsonian drugs is to decrease cholinergic influence in the basal ganglia

- They are used to reduce certain extrapyramidal effects caused by the antipsychotics. Drug-induced parkinsonism, dystonias and akinesia respond reasonably well, tremor less so and akathisia poorly.

Note: tardive dyskinesia can be made worse by these drugs.

Note: routine administration of antiparkinsonian drugs with antipsychotics is not generally favoured because:

- some patients develop adverse effects to the antiparkinsonian drug
- not all patients develop extrapyramidal adverse effects to antipsychotic drugs
- abuse of anticholinergic drugs is frequent.

Adverse effects (of Anticholinergic Drugs):

- Adverse effects are dose-related and most are due to anticholinergic actions
- Peripheral effects include: dryness of mouth, dilation of pupils, flushing, worsening of glaucoma, urinary hesitancy or obstruction, constipation, paralytic ileus, nausea and blurred vision.
- Central effects are dizziness, hallucinations, euphoria, hyperpyrexia and central excitation.
- Note: older persons are more susceptible to central adverse effects such as delirium.
- Benhexol appears to be the most likely to be abused because of its stimulating effects.

3.4 Bipolar Disorders and mood stabilising drugs

People who have bipolar disorder (sometimes called ‘manic-depressive disorder’) experience extreme mood swings from depression and sadness to elation and excitement. The mood swings tend to recur and can vary from mild to severe and can be of variable duration.

Early recognition and effective early treatment is vital to the present and future wellbeing of people with bipolar disorder. With effective treatment people can live full and productive lives.

Mania

The term 'mania' is used to describe the most severe state of extreme elation and overactivity. A small number of people with bipolar disorder experience only episodes of mania and do not experience depressive episodes.

Box 1: Treatment of acute presentation (Mania)

- Many patients with acute mania require hospitalisation for their protection. Insight is usually lacking and involuntary admission under the relevant health legislation may be required.
- Relapse in established bipolar disorder is often due to poor medication adherence, so serum concentrations should be checked where this is relevant. Other common causes of relapse include substance abuse (particularly marijuana), antidepressants or stressful life events.
- Initial treatment involves the commencement of Lithium, Sodium Valproate, Carbamazepine or a second-generation antipsychotic. There is usually a delay of onset of effect of 1 to 2-weeks. If the patient is on an antidepressant, this should be ceased.
- The containment of any associated behavioural disturbance such as aggression/violence, agitation/overactivity or disinhibition. This is essentially a means of calming or sedating the patient as an interim procedure until their mood stabilises. It usually involves temporary use of supplementary antipsychotics or benzodiazepines. The aim should be to gradually withdraw these medications once the mania settles.
- For prophylaxis use mood-stabilisers (Lithium, Carbamazepine or Sodium Valproate)

Medicines to treat manic-depressive or bipolar illnesses

Listed in the Fiji Essential Drug List:

Lithium Carbonate, (Tabs 250mg)

Carbamazepine (Tab 200mgs), Sodium Valproate (Elix 200mg/5mls, Tab 200mg),

One of three medicines can be used to treat bipolar disorder often in conjunction with the antipsychotic medications.

These medications usually need to be taken for a minimum of two years and require monitoring of the levels of medication in the blood. Ideally the decision to use these medications should be made by a specialist mental health professional.

Lamotrigine

Pharmacological properties

Lamotrigine stabilises presynaptic neuronal membranes by blockade of voltage-dependent sodium channels, preventing the release of excitatory neurotransmitters, particularly glutamate and aspartate.

Adverse effects and precautions

Adverse effects are primarily related to the central nervous system (dizziness, diplopia, ataxia, blurred vision, somnolence, insomnia). Tremor may be troublesome at high doses.

Lamotrigine can cause skin reactions of varying severity: a mild maculopapular rash; a more serious rash associated with fever, arthralgias and eosinophilia; severe and potentially fatal skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis. The risk of skin reactions is increased by concomitant Sodium Valproate therapy and/or rapid dose escalation. Lamotrigine doses should be increased gradually over 6 to 8 weeks. The initial dose should be lower and the rate of introduction should be more gradual in patients taking Sodium Valproate. Lamotrigine can precipitate Carbamazepine adverse effects, but plasma Carbamazepine concentration is not necessarily elevated.

Lithium Carbonate

i) Clinical indications

Primary use in Bipolar Affective Disorder and Unipolar Manic Disorder. Also used synergistically in treatment-resistant psychoses and in some personality disorders with unstable mood

ii) General:

Before commencing lithium, assess renal and thyroid function. Lithium is excreted by the kidney, and impaired renal function decreases lithium elimination and requires reduced doses.

Advise patients of likely adverse effects and the need for routine clinical and serum monitoring. Measure serum lithium concentrations every 3 to 6 months after stable therapeutic concentrations are achieved. Monitor renal function with serum creatinine and electrolytes every 3 to 6 months and thyroid function including TSH every 6 to 12 months in addition to clinical assessment.

iii) Use in children:

The diagnosis of 'juvenile (paediatric) bipolar disorder' in childhood or early adolescence is controversial when made in the absence of elevated mood, and largely premised on chronic irritability. There is little evidence to guide treatment of this presentation, with the symptoms frequently overlapping with Attention Deficit Hyperactivity Disorder (ADHD) and Oppositional Defiant Disorder. For the more classic euphoric form of the illness, which can occur (albeit uncommonly) in early to mid-adolescence, treatment is based on recommendations for adults

iv) Use in the elderly:

Use with caution in the elderly. Importance of careful monitoring of serum Lithium levels.

v) Use in pregnancy:

For the majority of patients with bipolar disorder, discontinuation of their treatment during pregnancy will result in relapse of their illness. The risks versus benefits must therefore be carefully weighed, taking into account the following, and mindful that polypharmacy should be avoided wherever possible due to substantial increases in teratogenic risk.

Mood stabilising drugs should usually be avoided in the first trimester. Thereafter, it would appear that Lithium is preferable to Valproate or Carbamazepine.

The use of lithium within the first trimester has, in many studies, been linked to foetal abnormalities. The benefits of lithium prophylaxis during pregnancy may, in some cases of severe bipolar disorder, outweigh the risks, and lithium has been considered as a first-line treatment during pregnancy for some such women. Nevertheless, lithium is not normally recommended during pregnancy.

In general, patients who are on lithium and who wish to become pregnant should be informed of the risk, and have their lithium **gradually** withdrawn before conception occurs. If the pregnant patient develops symptoms and is in need of pharmacological treatment, then antidepressants and antipsychotic drugs can be prescribed for depressive or manic symptoms, especially during the first trimester.

v) Side effects and (drug) interactions:

Note 1: Intercurrent illness, fluid loss or use of diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin II receptor blockers, or angiotensin converting enzyme (ACE) inhibitors may reduce renal clearance of lithium and lead to increased tissue concentrations and toxicity.

Note 2: Lithium toxicity:

Note: Patients and family or carers need to be educated to recognise symptoms of early lithium intoxication. In particular, patients should be warned that symptoms such as confusion, unsteadiness, nausea, diarrhoea or worsening tremor might indicate that their lithium dose requires adjustment.

Note 3: At supra-therapeutic concentrations lithium toxicity can cause: ataxia, vomiting, coarse tremor, disorientation, dysarthria, muscle twitches, impaired consciousness, acute renal failure and death. **Prolonged toxic concentrations may lead to irreversible brain damage.** Toxicity usually occurs at concentrations greater than 2 mmol/L, but may develop at considerably lower concentrations, especially in older persons.

The most important causes of lithium toxicity are:

- interactions with drugs that affect renal function (e.g. diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers)
- reduced fluid intake
- fluid loss from vomiting, diarrhoea or excessive sweating
- deliberate or inadvertent overdose.

Box 2: The general treatment guidelines for lithium toxicity are as follows:

- | |
|--|
| <ul style="list-style-type: none">• Withhold lithium until lithium blood levels are back in the therapeutic range and review lithium use when the toxicity syndrome settles.• For patients with serum lithium concentrations less than 3 mmol/L, give sufficient volume of saline infusion to produce an adequate diuresis (this is usually at least 3-litres per day)• if patients are either comatosed, in shock, severely dehydrated or have serum lithium concentrations of 3 mmol/L or more, renal dialysis is the treatment of choice. |
|--|

vi) Clinical notes of caution when using

Lithium should not be used where there are no facilities to test the levels of the drug in the blood. If no specialist laboratory facilities are available, Carbamazepine or Valproate are the better options to use. Note that none of these medications are ideal for women who are pregnant and a 'cost/benefit analysis needs to occur.

Baseline assessment of renal functions should be done prior to commencement.

vii) Dose ranges:

Lithium Carbonate 750 to 1000 mg orally, daily, in 2 or 3 divided doses or as a single dose at night. Serum concentrations should be determined after 5 to 7-days of steady dose treatment. The daily dose may be increased in increments of 250 to 500 mg depending on serum concentrations. The daily dose required to achieve therapeutic concentrations may range from 1000 to 2500 mg.

The therapeutic serum concentrations required in acute mania are higher than for maintenance therapy, and range from 0.8 to 1.2 mmol/L. The usual serum concentration may not be tolerated in older patients. Serum lithium concentrations should be estimated 12-hours after the last dose.

The margin separating therapeutic and toxic concentrations of this drug is narrow, and frequent regular serum lithium monitoring is required. Patients in their 60s or 70s may require only one-third to one-half the dose for young or middle-aged adults to obtain therapeutic serum concentrations.

Sodium Valproate

Sodium Valproate potentiates gamma-aminobutyric acid (GABA). Tremor, hair loss, sedation and appetite stimulation with weight gain are the commonest adverse effects. Gastrointestinal symptoms such as anorexia, nausea and vomiting can occur.

In acute mania, a plasma concentration of at least 300 micromol/L (43 mg/L) is necessary to benefit from Sodium Valproate, while toxicity is likely at concentrations of 850 micromol/L (122 mg/L) or higher. Within that range, dosage should be determined by clinical response.

Use:

Sodium Valproate 200 to 400 mg orally, twice daily. Dosage should be increased every 2 to 3-days by increments of 200 to 500 mg per day and plasma concentrations determined after 3-days of steady dose treatment. Alternatively, a loading dose strategy may be used, giving an initial oral dose of 20 mg/kg per day. Most patients require a regular daily dose of 1000 to 2000 mg, though some may need 3000 mg or higher.

Carbamazepine

Carbamazepine is an anti-epileptic and a useful mood-stabilizer. Dose-related adverse effects include sedation, headache, ataxia, dizziness, nausea and diplopia. Reversible mild leucopenia is common, but does not require discontinuation of therapy unless there is evidence of infection or the white cell count falls below 2×10^9 cells/L. Carbamazepine may potentiate bone marrow suppression if administered concurrently with other drugs that can cause agranulocytosis (e.g. Clozapine)

No therapeutic plasma concentration range for Carbamazepine in acute mania or maintenance for bipolar disorder has been established. In practice, therapeutic concentrations established for epilepsy, 20 to 50 micromol/L (5 to 12 mg/L), are used as a general guide. Due to hepatic microsomal enzyme induction by Carbamazepine (autoinduction), plasma concentrations may fall in the early stages of treatment. After dosage adjustment, autoinduction does not occur. It should be emphasised, however, that where clinical response is not evident and there is no evidence of major adverse effects, further increases in dosage may be required to achieve antimanic effect.

Use:

Carbamazepine 100 to 200 mg orally, twice daily. Dosage should be increased every 2 to 3-days by increments of 100 to 200 mg per day and plasma concentrations determined 5 to 7-days after achieving a dose of 400 to 800 mg. Some patients may need a regular daily dose of 1000 mg.

4.0 Management of behavioural and psychiatric emergency

Behavioural emergencies refer to situations where patients show behaviour that potentially places themselves or other people at risk of physical harm and requires immediate targeted intervention. The three main aetiological groups are:

- medical disorders, usually associated with delirium
- substance intoxication or withdrawal, with or without delirium
- psychiatric disorders.

Delirium is always a medical emergency and characterised by ‘confusion’ and loss of orientation. Check for head injury, drug history and OD. Pulse, BP, head-X Ray and monitoring pupils are all important. Refer to a medical clinician.

Substance intoxication or withdrawal is the more common and can be ascertained by history and signs and symptoms. Maintenance of airways, avoidance of choking and positional asphyxia are important. Time will resolve the emergency.

Psychiatric DOs will include Manic and Hypomanic states and psychotic DOs either from illness or from illicit substances. Occasionally Adjustment DO with Depression is seen after loss.

Note:

-It is always important to assess for ‘risk’ and maintain safety for both patient, other patients and for self and other staff (see chapter on risk)

-It is important to act within the legal framework and those treating an acutely disturbed person in such an emergency will need to be aware of the provisions of relevant legislation. Under ‘common law’, clinicians may use the principle of ‘duty of care’ as a basis for supporting an intervention, but must ensure that they are acting in accordance with professional guidelines and with due regard for good clinical judgment.

-It is very important to discern what category the emergency falls into. For this reason careful examination is important and a clear rationale for any intervention.

i) Non-pharmacological techniques to deal with behavioural emergencies:

-de-escalation strategies: a calm presence, pleasant non-threatening surrounding, language-appropriate approach;

-a 'show of force': have sufficient staff present to ensure safety;

-restraint: this should be taken as a last resort and can entail staff holding the patient or 'secluding' them in a purpose building facility.

ii) Pharmacological treatment for acute illness presentations:

IV:

Give Diazepam 2.5 to 5 mg increments IV, repeated every 3 to 4-minutes until the required level of rousable drowsiness is obtained, up to a maximum of 20 to 30 mg. Then seek further medical advice;

Or, give Droperidol 5 to 10 mg IV, up to maximum dose of 20 mg before consultation

IM:

Give (if obtainable), Midazolam 10 to 15 mg IM.

It will be necessary to continue physical restraint until the pharmacological effect is apparent. Intravenous access may then be established. Do not use doses less than 10 mg because these will not be effective.

Use of Haloperidol and Chlorpromazine in Behavioural Emergencies

(Source: Therapeutic Guidelines Psychotropic, Version 5)

In many cases the urgent need in behavioural emergencies is to achieve sedation to:

- Reduce the risk of people harming themselves or others
- Allow diagnostic assessment to proceed
- Allow transport to an appropriate treatment setting

Special Points to Remember in Using Sedating Medications

- Benzodiazepines are the drug of choice (as they are more sedating and have fewer adverse effects than antipsychotics)
- Antipsychotics should only be considered if any of the following are present: (1) Patient's behaviour suggest psychotic symptoms are present; (2) there is intense agitation, including subjective turmoil; (3) there is high risk of severe and immediate physical danger; (4) adequate sedation is not achieved with a benzodiazepine alone.

- Use oral route whenever possible
- Vital signs and mental state should be monitored closely during and after sedative administration
- Aim to achieve an appropriate level of sedation quickly by using sufficient medication initially
- Do not give diazepam intramuscularly as absorption is poor and erratic (better to use midazolam)
- Avoid if possible giving parenteral chlorpromazine as it can cause catastrophic hypotension, abscess formation (IM use) and sudden death (IV use)
- Elderly patients, especially if frail may require doses of medications lower than the recommended range; benzodiazepines (especially long-acting) should be avoided

NB. Parenteral sedation should only be administered under conditions in which monitoring of vital signs is possible, personnel are trained in cardiopulmonary resuscitation techniques and appropriate monitoring and resuscitation equipment is immediately available.

Haloperidol

1.5 to 5 mg orally repeated every two hours titrated to a clinical response, up to 10 mg in 24 hours

(may require benzhexol 2 mg orally or benztropine 2 mg IMI if EPSE develop)

Or

2.5 to 5 mg IMI (with benztropine injection 2 mg IMI to avoid EPSE especially acute dystonias) to a maximum of 10 mg/24 hours

Chlorpromazine (can be used in place of haloperidol except if delirium is suspected)

50 to 200 mg orally repeated every 2 hours, titrated to a clinical response, up to 400 mg in 24 hours

Or

50 to 100 mg IMI (deep injection) (up to 8-12 hourly in the first 24 hours)

(Need to monitor vitals especially BP closely after each injection as outlined above). The Parenteral use of chlorpromazine outlined above is what is practiced at St. Giles.

Note:

-Patient deaths have been recorded due to excessive dosage of antipsychotics coupled with 'vaso-vagal hyper-drive' whereby stimulation causes the heart to cease beating.

-The use of poly-pharmacy is to be discouraged. Use one drug in effective dosage

Box 3 Special points in tranquillisation in psychiatric settings

- Use the oral route of administration whenever possible.
- Closely monitor vital signs and mental state during and after administration of medication.
- If doses outside the guidelines appear to be required, consult a psychiatrist, emergency physician or anaesthetist.
- Aim to achieve an appropriate level of calmness quickly by using sufficient medication initially: repeated sub therapeutic doses may lead to insufficient behavioural control and greater total doses of medication.
- Do not give diazepam by intramuscular injection, as absorption is poor and erratic.
- Do not give parenteral chlorpromazine, as it can cause catastrophic hypotension, abscess formation (IM use) and sudden death (IV use).
- Do not give Midazolam by intravenous injection owing to the risk of respiratory depression.
- Use benzodiazepines with particular caution in patients with significant respiratory impairment, e.g. chronic obstructive pulmonary disease (COPD).
- Accurately record repeat doses.
- Older patients, particularly if frail, may require doses of medications lower than the recommended range; avoid benzodiazepines (especially if long-acting) if possible in this group: repeated doses are likely to result in cumulative effects that may prove dangerous to the patient
- The principles of treatment for older children and adolescents are generally the same as for adults.
- Parenteral (IM or IV) medication in children is an intervention that should be undertaken under the supervision of specialist child psychiatrists or paediatricians, and only in a medical setting where staff are trained in resuscitation procedures and have immediate access to resuscitation and monitoring equipment.
- When considering restraint procedures and drug selection, take into account the possibility that female patients may be pregnant and conduct a test for pregnancy as soon as is practicable.
- Keep a record of medications administered to the patient; it should travel with the patient if they are transferred to another facility.
- Accurately record details of restraint, medication administered and monitoring procedures.
- Frequent administration of 'as needed' (PRN) medication for more than 24-hours usually indicates an inadequate regimen of regular medication. There is evidence that frequent PRN IM injections of antipsychotic medication, especially when used over extended periods of time increase the risk of neuroleptic malignant syndrome and assaults upon nursing staff.

5.0 General Information on psychotropic drugs

i) Summary

Table 9 – Summary of medications used to treat mental illness

Medication	Condition	Indicative recommended dosage range ³	Availability in the Pacific region	WHO essential list ⁴	Maximum dosage and other comments
Alprazolam	Anxiety States	Adult- anxiety 0.25mg-0.5mg three times a day; depression 0.5mg three times a day range 1.5mg-4.5mg in divided dose.		No	Generally safe in over-dosage but highly addictive
<i>Amitriptyline hydrochloride</i>	Depression	Adult 75mg/daily; may increase to max. 150mg/day Maintenance 50-100mg/day	Available in Tokelau, Fiji, Palau, Samoa, Kiribati	Yes: tablet 25mg	Can be used up to 300/day but needs close monitoring for SE's
Benztropine	Prevents acute dystonias	2mg tab and 1 mg/1ml	Available in Samoa, Fiji		Titrate for effect. Max 2mg tds
Bupropion			Available in Palau, CNMI	No	
Camphetamine / Dextroamphetamine			Available in CNMI	No	
<i>Carbamazepine</i>	Partial, generalised and mixed seizures	100-200mg 1-2 times daily up to 400mg 2-3 times daily max 2,00mg/day.	Available in Tokelau, Fiji, Palau, Niue, Samoa, Kiribati	Yes tablet (scored) 100mg; 200mg	
<i>Carbidopa</i>	Treatment of Parkinson syndrome		Available in Fiji	Yes tablet 100mg+10mg; 250mg+25mg	
<i>Chlorpromazine hydrochloride</i>	Psychosis, mania, schizophrenia	Adults 25mg 3 times daily, 75mg-300mg maximum daily dosage	Available in Tokelau, Fiji, Palau, Samoa, Kiribati	Yes: Injection 25mg/ml in 2-ml ampoule Oral liquid 25 mg/5ml Tablet 100mg	Can be given in high doses but beyond 500mg consider other medication
Citalopram hydrochloride	SSRI Depression	Adults once daily initially 20mg/day	Available in CNMI	No	

³ Important that up to date information is accessed in consultation with pharmaceutical expertise through New Ethicals (www.mims.co.nz). Contact your local WHO office for further advice about pharmaceutical expertise

⁴ World Health Organization. 2007. *WHO Model List of Essential Medicines* (15th List). Available at: www.who.int/medicines/publications/EML15.pdf.

Medication	Condition	Indicative recommended dosage range ³	Availability in the Pacific region	WHO essential list ⁴	Maximum dosage and other comments
		max 60mg/day			
Clomipramine hydrochloride	Obsessive compulsive disorder and panic attacks			Yes capsule 10 mg; 25mg	
Clonazepam	Epilepsy	1.5mg/day max 20mg/day	Available in Tokelau, Palau, Samoa	No	
Clozapine	Schizophrenia	Protocols around this drug must be adhered to when prescribing	Available in Samoa	No	Not available in Fiji. Must be closely monitored by serum assay
Desipramine				No	
Dexedrine			Available in CNMI	No	
<i>Diazepam</i>	Acute alcohol withdrawals; generalised anxiety and sleep disorders	Adult 2 mg 3 times day, max 30mg/day	Available in Tokelau, Fiji, Palau, Niue, Samoa, Kiribati	Yes tablet (scored) 2mg; 5mg	No limit and very safe. Addictive with prolonged use
Dothiepin hydrochloride	Depression and assoc anxiety	Adult 75 mg/day as single or divided dose; may increase to 150mg/day; max 225mg/day	Available in Tokelau	No	See other TCA's
Ethosuximide	Anticonvulsant		Available in Fiji	Yes: <ul style="list-style-type: none"> capsule 250mg oral liquid 250mg/5ml 	
<i>Fluoxetine hydrochloride</i>	Depression and assoc anxiety; psychotic disorders	Adult; initially 20mg/day; 80mg/day Bulimia nervosa 60mg/day; OCD 20-60mg/day	Available in Tokelau, Palau, Samoa	Yes: capsule or tablet 20mg	Max dose for depression 20-40mg/day. For anxiety DO up to 80mg/day
<i>Fluphenazine</i>	Antipsychotic	12.5-25mg IMI; max 100mg, 4 weekly	Available in Fiji, Palau, Samoa	Yes injection 25mg (Decanoate or Enantate) in 1-ml ampoule	
Fluvoxamine				No	
<i>Haloperidol</i>	Psychotic Disorders	1-15mg depending on severity of symptoms	Available in Fiji, Palau, Samoa, Kiribati	Yes: <ul style="list-style-type: none"> Injection 5mg in 1-ml 	High doses can be tolerated but come with a 'cost' (of SE's)

Medication	Condition	Indicative recommended dosage range ³	Availability in the Pacific region	WHO essential list ⁴	Maximum dosage and other comments
				ampoule • Tablet 2mg, 5mg	such as Tardive Dyskinesia)
<i>Imipramine hydrochloride</i>	Depression	Adult 25mg 1-3 times daily; gradual increase to 150-200mg/day, maintenance usually 50-100mg daily	Available in Palau	No?	See TCA's
Levodopa benserazida	Treatment of Parkinson syndrome	12.5mg 3-4 times a day	Available in Fiji, Niue	Yes tablet 100mg+10mg; 250mg+25mg	
<i>Lithium carbonate</i>	Mania, hypomania, (bipolar disorder)	Adults (70kg) 400-1,200 daily in 1-2 divided dosage. Regular renal function and blood level required.	Available in Fiji, Palau, Samoa	Yes capsule or tablet 300mg	Dangerous SE's beyond 1.2mm/L Therefore monitor
Lorazepam	Moderate to severe anxiety	2-3mg/day divided range 1-10 mg/day	Available in Palau	No	
Methadone	Substance dependence programmes			Yes: • concentrate for oral liquid 5mg/ml; 10 mg/ml (hydrochloride) • oral liquid 5mg/5ml; 10 mg/5ml Should only be used within an established support programme	Max dose should be about 130mgs/day
Methylphenidate	Attention deficit disorder		Available in Palau, Samoa	No	
Nitrazepam	Nervous or organic sleep disturbances	Adults 5-10mg before retiring	Available in Tokelau, Niue	No	A safe tranquillizer even in OD
Norimipramine				No	

Medication	Condition	Indicative recommended dosage range ⁵	Availability in the Pacific region	WHO essential list ⁶	Maximum dosage and other comments
<i>Olanzapine</i>	Antimanic, mood stabiliser, schizophrenia	5-10mg /day	Available in Fiji (limited to 1000 10mg tablets per month), CNMI, Samoa	No	Severe SE's profile. Use with caution and strict monitoring
Oxazepam	Anxiety	Adult 10-30mg 3-4 times daily	Available in Palau	No	
Paroxetine hydrochloride	Depression and assoc anxiety; OCD; PTSD	Adult commence once daily increase by 10mg 20mg/day up to 40mg/day,	Available in CNMI	No	See SSRI's
Pemoline			Available in CNMI	No	
<i>Phenytoin sodium</i>	Grand mal and psychomotor seizures	Adults Initially 4-5mg/kg/day max 600mg. Blood monitoring required	Available in Fiji, Tokelau, Palau, Niue, Kiribati	Yes: <ul style="list-style-type: none"> capsule 25mg; 50 mg; 100mg injection 50mg/ml in 5-ml vial Oral liquid* 25mg; 50mg; 100mg Tablet (chewable) 50mg. * The presence of both 25mg/5ml and 30mg/5ml strengths on the same market would cause confusion in prescribing and dispensing and should be avoided	

⁵ Important that up to date information is accessed in consultation with pharmaceutical expertise through New Ethicals (www.mims.co.nz). Contact your local WHO office for further advice about pharmaceutical expertise

⁶ World Health Organization. 2007. *WHO Model List of Essential Medicines* (15th List). Available at: www.who.int/medicines/publications/EML15.pdf.

Medication	Condition	Indicative recommended dosage range ⁷	Availability in the Pacific region	WHO essential list ⁸	Maximum dosage and other comments
<i>Propranolol hydrochloride</i>	Prophylaxis		Available in Samoa, Fiji	Yes tablet 20 mg: 40 mg	
Provigil			Available in CNMI	No	
Risperidone	Psychotic disorders	2-6mg/day may be divided	Available in CNMI, Samoa	No	
Sertraline			Available in CNMI	No	
<i>Sodium Valproate</i>	Anticonvulsant, antipsychotic, bipolar disorder	Adult 2 divided dosages 600mg/day range 1,000mg-2000mg/day	Available in Fiji, Palau, Niue, Samoa, Kiribati	Yes: <ul style="list-style-type: none"> • tablet (enteric-coated) 200mg, 500mg • oral liquid 200mg/5ml • tablet (crushable) 100mg 	
Trifluoperazine	Psychoses	1.5-5 mgs TDS	Fiji	No	
Venlafaxine hydrochloride	Major Depression	Adults usually 37.5mg twice daily, may increase to 75mg twice daily after several weeks.		No	
Zuclopenthixol	Psychotic disorders		Samoa		

⁷ Important that up to date information is accessed in consultation with pharmaceutical expertise through New Ethicals (www.mims.co.nz). Contact your local WHO office for further advice about pharmaceutical expertise

⁸ World Health Organization. 2007. *WHO Model List of Essential Medicines (15th List)*. Available at: www.who.int/medicines/publications/EML15.pdf.

ii) What if the medicines do not work?

There are several reasons why a medication may not produce the desired effects.

Reasons why the medicine may not work

- Non-compliance. Has the person understood the correct dosage and reason for taking the medicine? People may not take medicines appropriately if they think they feel better and no longer need it. They also might become worried about side effects or about becoming addicted and not relaying this to the prescriber.
- Insufficient dose. This is particularly important in the case of antidepressants, which are often prescribed in too small a dose.
- Medicines not taken for long enough to be effective. This occurs mainly in relation to antidepressants. This is because they take at least two weeks before they become effective
- Wrong diagnosis. People may be withdrawn and tired because they are depressed, or in some cases when they are psychotic. An antidepressant will not help a person who is psychotic. Reconsideration of the diagnosis may be necessary but only if you are sure that the person has been taken the recommended dosage for at least a month.
- Medical conditions such as diarrhoea (and poor absorption) or liver disease

6.0 Bibliography

Australian Medical Association (2004) *Code of Ethics*. Melbourne

Australian Nursing Council, Royal College of Nursing, & Australia, Australian Nursing Federation (2002). *Code of Ethics for Nurses in Australia*. Canberra:

Commonwealth of Australia (2001). *Code of Ethics and Guide to Ethical Conduct for Patients/clients Aged Care [Publication No. 2895]*. Canberra, ACT: Commonwealth Department of Health & Aged Care.

Crabb, J and Razi, E. 2007. *Essential Skills for Mental Health Care*. Basic Needs, Ghana.

McDonald, D., & Jowitt, A. 2000. Kava in the Pacific Islands: a contemporary drug of abuse? *Drug and Alcohol Review*, 19(2):217-227.

Mental Health and Workforce Division of the Australian Government Department of Health and Ageing. *What is a depressive disorder?* Canberra: Department of Health and Ageing.

Mental Health and Workforce Division of the Australian Government Department of Health and Ageing *What is an anxiety disorder?* Canberra: Department of Health and Ageing.

Mental Health and Workforce Division of the Australian Government Department of Health and Ageing. *What is a mental illness?* Canberra: Department of Health and Ageing.

Patel, V. 2003. *Where there is no psychiatrist: a mental health care manual*. Gaskell: Royal College of Psychiatrists, Glasgow, UK.

Therapeutic Guidelines Psychotropic Series 6 2008 Victoria, Australia

The Royal Australian and New Zealand College of Psychiatrists. 2005. *Anorexia Nervosa: New Zealand Treatment Guide for Consumers and Carers*. Wellington: The Royal Australian and New Zealand College of Psychiatrists.

The Royal Australian and New Zealand College of Psychiatrists. 2005. *Bipolar Disorder: New Zealand Treatment Guide for Consumers and Carers*. Wellington: The Royal Australian and New Zealand College of Psychiatrists.

The Royal Australian and New Zealand College of Psychiatrists. 2005. *Panic Disorder and Agoraphobia: New Zealand Treatment Guide for Consumers and Carers*. Wellington: The Royal Australian and New Zealand College of Psychiatrists.

The Royal Australian and New Zealand College of Psychiatrists. 2005. *Schizophrenia: New Zealand Treatment Guide for Consumers and Carers*. Wellington: The Royal Australian and New Zealand College of Psychiatrists.

The Royal Australian and New Zealand College of Psychiatrists. 2005. *Self Harm: New Zealand Treatment Guide for Consumers and Carers*. Wellington: The Royal Australian and New Zealand College of Psychiatrists.

Tiller JWG. 1998 Medicinal mishaps. *Aust Prescriber*; 21:63.

UK Central Council for Nursing, Midwifery and Health Visiting (1998). *Guidelines for Mental Health and Learning Disability Nursing – a guide to working with and valuing clients*. London:

United Nations (2006). *Convention on the Rights of Persons with Disabilities*. NY:

World Health Organization. 2000. *Preventing Suicide: A Resource for General Practitioners*. WHO: Geneva.

World Health Organization. 2007b. *Mental Health* (available at http://www.who.int/mental_health/en/)

World Health Organization. 2007. *International Statistical Classification of Diseases and Related Health Problems*. WHO (available at <http://www.who.int/classifications/apps/icd/icd10online/>)

World Health Organization. 2007. *Suicide Prevention*. World Health Organization (available at www.who.int/mental_health/prevention/suicide/suicideprevent/en/)

World Health Organization. 2007. *WHO Model List of Essential Medicines*. Available at: www.who.int/medicines/publications/EML15.pdf