Psychotherapeutic drugs

Drugs used in psychotic disorders

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 (for example chlorpromazine), butyrophenones (for example haloperidol), thioxanthenes (for example 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).

ACUTE PHASE TREATMENT

The administration of **chlorpromazine** or **haloperidol** will relieve symptoms such as thought disorder, hallucinations and delusions and prevent relapse. They are usually less effective in apathetic, withdrawn patients. However, haloperidol may restore an acutely ill schizophrenic, who was previously withdrawn, or even mute and akinetic, to normal activity and social behaviour. In the acute phase chlorpromazine may be administered by intramuscular injection in a dose of 25–50 mg which can be repeated every 6–8 hours while observing the patient for possible hypotension. In most cases, however, the intramuscular injection is not needed and patients can be treated with an oral dose. Haloperidol may be administered in the acute phase.

MAINTENANCE THERAPY

Long-term treatment in patients with a definite diagnosis of schizophrenia may be necessary after the first episode to prevent the manifest illness from becoming chronic.

The lowest possible dose of antipsychotic drug that will prevent major exacerbations of florid symptoms is used for long-term management. Too rapid a dose reduction should be avoided. Intramuscular depot preparations such as **fluphenazine decanoate** may be used as an alternative to oral maintenance therapy especially when compliance with oral treatment is unreliable. Exacerbations of illness in patients on maintenance drug therapy can be precipitated by stress.

Withdrawal of maintenance drug treatment requires careful surveillance since it is not possible to predict the course of the disease and the patient may suffer a relapse if treatment is withdrawn inappropriately. Further, the need for continuation of treatment may not be evident on withdrawal of treatment because relapse may be delayed for several weeks.

ADVERSE EFFECTS

They are 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 patients over 70 years of age.

Extrapyramidal symptoms are the most troublesome and are caused most frequently by the piperazine phenothiazines such as fluphenazine, the butyrophenones such as 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 of an antipsychotic, particularly in elderly patients (see section 9.2). 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.

Neuroleptic malignant syndrome (hypothermia, fluctuating levels of consciousness, muscular rigidity, and autonomic dysfunction with pallor, tachycardia, labile blood pressure, sweating and urinary incontinence) is a rare adverse effect of haloperidol and chlorpromazine. It is managed by discontinuing the antipsychotic, correcting fluid and electrolyte defects, and giving bromocriptine and sometimes dantrolene.

Chlorpromazine hydrochloride

Chlorpromazine is a representative antipsychotic. Various drugs can serve as alternatives

WARNING. Owing to the risk of contact sensitization, pharmacists, nurses, and other health workers should avoid direct contact with chlorpromazine; tablets should not be crushed and solutions should be handled with care

Tablets , chlorpromazine hydrochloride 100 mg

Syrup , chlorpromazine hydrochloride 25 mg/5 ml

Injection (Solution for injection), chlorpromazine hydrochloride 25 mg/ml, 2-ml ampoule

Uses:

schizophrenia and other psychotic disorders, mania, psychomotor agitation and violent behaviour; adjunct in severe anxiety

Contraindications:

impaired consciousness due to CNS depression; bone-marrow depression; phaeochromocytoma

Precautions:

cardiovascular and cerebrovascular disorders, respiratory disease, parkinsonism, epilepsy, acute infections, pregnancy (Appendix 2), breastfeeding (Appendix 3), renal and hepatic impairment (avoid if severe; Appendices 4 and 5), history of jaundice, leukopenia (blood counts if unexplained fever or infection); hypothyroidism, myasthenia gravis, prostatic hypertrophy, angle-closure glaucoma; elderly (particularly in very hot or very cold weather); avoid abrupt withdrawal; patients should remain supine and the blood pressure monitored for 30 minutes after intramuscular injection; **interactions:** Appendix 1

SKILLED TASKS.	May impair ability to perform skilled tasks, for example operating machinery, driving

Dosage:

Schizophrenia and other psychoses, mania, psychomotor agitation, violent behaviour, and severe anxiety (adjunct), *by mouth* , **ADULT** initially 25 mg 3 times daily (*or* 75 mg at night) adjusted according to response to usual maintenance dose of 100–300 mg daily (but up to 1.2 g daily may be required in psychoses); **ELDERLY** (or debilitated) third to half adult dose; **CHILD** (childhood schizophrenia and autism) 1–5 years 500 micrograms/kg every 4–6 hours (maximum 40 mg daily); 6–12 years, third to half adult dose (maximum 75 mg daily)

For relief of acute symptoms, *by deep intramuscular injection* , **ADULT** 25–50 mg every 6–8 hours; **CHILD** 500 micrograms/kg every 6–8 hours (1–5 years, maximum 40 mg daily; 6–12 years, maximum 75 mg daily) (see also Precautions and Adverse effects)

Adverse effects:

extrapyramidal symptoms and on prolonged administration, occasionally potentially irreversible tardive dyskinesias (see notes above); hypothermia (occasionally pyrexia), drowsiness, apathy, pallor, nightmares, dizziness, excitement, insomnia, headache, confusion, depression; more rarely, agitation, EEG changes, convulsions, nasal congestion; anticholinergic symptoms including dry mouth, constipation, blurred vision, difficulty in micturition; hypotension, tachycardia and arrhythmias; ECG changes; respiratory depression; menstrual disturbances, galactorrhoea, gynaecomastia, impotence, weight gain; sensitivity reactions such as agranulocytosis, leukopenia, leukocytosis, haemolytic anaemia, photosensitization, contact sensitization and rashes, jaundice and alterations in liver function; neuroleptic malignant syndrome; lupus erythematosus-like syndrome; with prolonged high

dosage, corneal and lens opacities, and purplish pigmentation of the skin, cornea and retina; intramuscular injection may be painful and cause hypotension and tachycardia (see Precautions) and nodule formation

Haloperidol

Haloperidol is a representative antipsychotic. Various drugs can serve as alternatives

Tablets , haloperidol 2 mg, 5 mg

Injection (Solution for injection), haloperidol 5 mg/ml, 1-ml ampoule

Uses:

schizophrenia and other psychotic disorders, mania, psychomotor agitation and violent behaviour; adjunct in severe anxiety

Contraindications:

impaired consciousness due to CNS depression; bone-marrow depression; phaeochromocytoma; porphyria; basal ganglia disease

Precautions:

cardiovascular and cerebrovascular disorders, respiratory disease, parkinsonism, epilepsy, acute infections, pregnancy (Appendix 2), breastfeeding (Appendix 3), renal and hepatic impairment (avoid if severe; Appendices 4 and 5), history of jaundice, leukopenia (blood count required if unexplained fever or infection); hypothyroidism, myasthenia gravis, prostatic hypertrophy, angle-closure glaucoma; also subarachnoid haemorrhage and metabolic disturbances such as hypokalaemia, hypocalcaemia, or hypomagnesaemia; elderly (particularly in very hot or very cold weather); children and adolescents; avoid abrupt withdrawal; patients should remain supine and the blood pressure monitored for 30 minutes after intramuscular injection; **interactions:** Appendix 1

SKILLED TASKS.	May impair ability to perform skilled tasks, for example operating machinery, driving

Dosage:

Schizophrenia and other psychoses, mania, psychomotor agitation, violent behaviour, and severe anxiety (adjunct), *by mouth* , **ADULT** initially 1.5–3 mg 2–3 times daily *or* 3–5 mg 2–3 times daily in severely affected or resistant patients (up to 30 mg daily in resistant schizophrenia); **ELDERLY** (or debilitated) initially half adult dose; **CHILD** initially 25–50 micrograms/kg daily in 2 divided doses (maximum 10 mg daily)

Acute psychotic conditions, *by intramuscular injection* , **ADULT** initially 2–10 mg, subsequent doses every 4–8 hours according to response (up to every hour if necessary) to total maximum of 18 mg; severely disturbed patients may require initial

dose of up to 18 mg; **elderly** (or debilitated) initially half adult dose; **CHILD** not recommended

Adverse effects:

as for Chlorpromazine Hydrochloride (see above), but less sedating and fewer hypotensive and anticholinergic symptoms; pigmentation and photosensitivity reactions rare; extrapyramidal symptoms are common, particularly acute dystonia and akathisia (especially in thyrotoxic patients); rarely weight loss, hypoglycaemia, inappropriate antidiuretic hormone secretion

Fluphenazine

Fluphenazine is a representative depot antipsychotic, used if compliance unlikely to be reliable. Various drugs can serve as alternatives

Oily injection (Solution for injection), fluphenazine decanoate 25 mg/ml, 1-ml ampoule

Oily injection (Solution for injection), fluphenazine enantate 25 mg/ml, 1-ml ampoule

Uses:

maintenance treatment of schizophrenia and other psychoses

Contraindications:

children; confusional states; impaired consciousness due to CNS depression; parkinsonism; intolerance to antipsychotics; depression; bone-marrow depression; phaeochromocytoma

Precautions:

treatment requires careful monitoring for optimum effect; initial small test dose as adverse effects are prolonged; extrapyramidal symptoms occur frequently; when transferring from oral to depot therapy, dosage by mouth should be reduced gradually; cardiovascular and cerebrovascular disorders, respiratory disease, epilepsy, acute infections, pregnancy (Appendix 2), breastfeeding (Appendix 3), renal and hepatic impairment (avoid if severe; Appendices 4 and 5), history of jaundice, leukopenia (blood counts if unexplained fever or infection); hypothyroidism, myasthenia gravis, prostatic hypertrophy, angle-closure glaucoma; elderly (particularly in very hot or very cold weather); **interactions:** Appendix 1

SKILLED TASKS.	May impair ability to perform skilled tasks, for example operating machinery, driving

Dosage:

Maintenance in schizophrenia and other psychoses, *by deep intramuscular injection* into gluteal muscle, **ADULT** test dose of 12.5 mg (6.25 mg in elderly), then after 4–7 days 12.5–100 mg repeated at intervals of 2–5 weeks, adjusted according to response; **CHILD** not recommended

ADMINISTRATION. According to manufacturer's directions

Adverse effects:

as for Chlorpromazine Hydrochloride (see above), but less sedating and fewer hypotensive and anticholinergic symptoms; higher incidence of extrapyramidal symptoms (most likely to occur a few hours after injection and continue for about 2 days but may be delayed); systemic lupus erythematosus; pain at injection site, occasionally erythema, swelling, nodules

Drugs used in mood disorders

Mood disorders can be classified as depression (unipolar disorder) and mania; alternating episodes of mania and depression (manic depression) are termed bipolar disorder.

Electroconvulsive therapy (ECT) has been shown to be rapidly effective in the urgent treatment of severe depression. Counselling and psychotherapy have an important role in treating some forms of depression.

Drugs used in depressive disorders

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 it may result in enhanced adverse effects or 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 may be used as an alternative for maintenance treatment (see section 24.2.2). 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 amtimuscarinic) 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 because they are dangerous in overdose.

The SSRIs characteristically cause gastrointestinal disturbances, 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. The 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.

Amitriptyline hydrochloride

Amitriptyline hydrochloride is a representative tricyclic antidepressant. Various drugs can serve as alternatives

Tablets , amitriptyline hydrochloride 25 mg

Uses:

moderate to severe depression

Contraindications:

recent myocardial infarction, arrhythmias (especially heart block); manic phase in bipolar disorders; severe liver disease; children; porphyria

Precautions:

cardiac disease (see Contraindications above), history of epilepsy; pregnancy (Appendix 2); breastfeeding (Appendix 3); elderly; hepatic impairment (Appendix 5); thyroid disease; phaeochromocytoma; history of mania, psychoses (may aggravate psychotic symptoms); angle-closure glaucoma, history of urinary retention; concurrent electroconvulsive therapy; avoid abrupt withdrawal; anaesthesia (increased risk of arrhythmias and hypotension); **interactions:** Appendix 1

SKILLED TASKS.	May impair ability to perform skilled tasks, for example operating machinery, driving

Dosage:

Depression, *by mouth* , **ADULT** initially 75 mg (elderly and adolescents 30–75 mg) daily in divided doses *or* as a single dose at bedtime increased gradually as necessary to 150–200 mg daily; **CHILD** under 16 years not recommended for depression

Adverse effects:

sedation, dry mouth, blurred vision (disturbance of accommodation, increased intra-ocular pressure), constipation, nausea, difficulty in micturition; cardiovascular adverse effects particularly with high dosage including ECG changes, arrhythmias, postural hypotension, tachycardia, syncope; sweating, tremor, rash and hypersensitivity reactions (urticaria, photosensitivity); behavioural disturbances; hypomania or mania, confusion (particularly in elderly), interference with sexual function, blood sugar changes; increased appetite and weight gain (occasional weight loss); endocrine adverse effects such as testicular enlargement, gynaecomastia and galactorrhoea; convulsions, movement disorders and dyskinesias, fever, agranulocytosis, leukopenia, eosinophilia, purpura, thrombocytopenia, hyponatraemia (may be due to inappropriate antidiuretic hormone secretion); abnormal liver function test

In overdose, excitement, restlessness, marked anticholinergic effects; severe symptoms including unconsciousness, convulsions, myoclonus, hyperreflexia, hypotension, acidosis, respiratory and cardiac depression with arrhythmias

Drugs used in bipolar disorders

Treatment of bipolar disorders has to take account of three stages: treatment of the acute episode, continuation phase and prophylaxis to prevent further episodes. **Lithium** is effective in acute mania but symptomatic control of the florid symptoms with an antipsychotic or benzodiazepine is often necessary whilst waiting for the antimania drug to exert its effect. Benzodiazepines may be given during the initial stages until lithium becomes effective but they should not be used for long periods because of the risk of dependence. Lithium may be given concurrently with antipsychotics and treatment with the antipsychotic should be tailed off as lithium becomes effective. Alternatively, lithium therapy may be delayed until the patient's mood is stabilized with the antipsychotic. However, there is a risk of neurotoxicity and increased extrapyramidal disorders when lithium and antipsychotics are used concurrently (Appendix 1). Lithium is the mainstay of treatment but its narrow therapeutic range is a disadvantage. **Sodium valproate** is effective and **carbamazepine** may also be used.

Treatment of depressive episodes in bipolar disorders will mostly involve combination treatment using either lithium or sodium valproate together with a tricyclic antidepressant. Increased adverse effects are a problem which may compromise treatment.

Lithium prophylaxis should usually only be undertaken with specialist advice and the likelihood of recurrence considered. Long-term lithium therapy has been associated with thyroid disorders and mild cognitive and memory impairment. Patients should continue the treatment for longer than 3 to 5 years only if benefit persists.

Withdrawal appears to produce high levels of relapse. If lithium is to be discontinued, the dose should be reduced gradually over a few weeks and patients should be warned of possible relapses if discontinued abruptly.

Lithium salts have a narrow therapeutic/toxic ratio and should only be prescribed if there are facilities for monitoring serum lithium concentrations. Doses are adjusted to achieve serum-lithium concentrations of 0.4–1 mmol/litre (lower end of range for maintenance therapy and the elderly) on samples taken 12 hours after the preceding dose. The optimum range for each patient should be determined.

Overdosage, usually with serum-lithium concentration of over 1.5 mmol/litre may be fatal and toxic effects include coarse tremor, ataxia, dysarthria, nystagmus, renal impairment and convulsions. If any of these effects occur, treatment should be stopped, serum-lithium concentration determined and in mild overdosage large amounts of sodium and fluid should be given to reverse the toxicity; in severe toxicity, haemodialysis may be required.

For patients who are unresponsive to or intolerant of lithium, carbamazepine may be used in the prophylaxis of bipolar illness particularly in those with rapid cycling affective disorders (more than four affective episodes per year).

Lithium carbonate

Tablets , *capsules* , lithium carbonate 300 mg

Uses:

treatment and prophylaxis of mania, prophylaxis of bipolar disorder and recurrent depression

Contraindications:

renal impairment (Appendix 4); cardiac insufficiency; conditions with sodium imbalance such as Addison disease

Precautions:

measure serum-lithium concentration about 4 days after starting treatment, then weekly until stabilized, then at least every 3 months; monitor thyroid function every 6–12 months on stabilized regimens—risk of hypothyroidism (see below); monitor renal function; maintain adequate fluid and sodium intake; reduce dose or discontinue in diarrhoea, vomiting and intercurrent infection (especially if associated with profuse sweating); pregnancy (Appendix 2); breastfeeding (Appendix 3); elderly (reduce dose); diuretic treatment, myasthenia gravis; surgery; if possible, avoid abrupt withdrawal (see notes above); **interactions:** Appendix 1

Patient Advice. Patients should maintain adequate fluid intake and should avoid dietary changes which may reduce or increase sodium intake. Patients should be advised to seek medical attention if symptoms of hypothyroidism (for example, feeling cold, lethargy) develop (women are at greater risk)

NOTE. Different preparations vary widely in bioavailability; a change in the preparation used requires the same precautions as initiation of treatment

Dosage:

Treatment of mania (general guidelines only, see also note below) *by mouth* , **ADULT** initially 0.6–1.8 g daily (elderly 300–900 mg daily)

Prophylaxis of mania, bipolar disorder and recurrent depression (general guidelines only, see also note below), *by mouth* , **ADULT** initially 0.6–1.2 g daily (elderly 300–900 mg daily)

NOTE. Dosage of lithium depends on the preparation chosen since different preparations vary widely in bioavailability. Dosage should be adjusted to achieve a serum-lithium concentration of 0.4–1 mmol/litre (lower end of range for maintenance therapy and in elderly) on samples taken 12 hours after a dose and 4–7 days after starting treatment then every week until dosage has remained unchanged for 4 weeks, then every 3 months thereafter

DOSAGE REGIMENS. For dose information for a specific preparation, consult manufacturer's literature

Adverse effects:

gastrointestinal disturbances, fine tremor, renal impairment (particularly impaired urinary concentration and polyuria), polydipsia, weight gain and oedema (may respond to dose reduction); hyperparathyroidism and hypercalcaemia reported; signs of intoxication include blurred vision, muscle weakness, increasing gastrointestinal disturbances (anorexia, vomiting, diarrhoea), increased CNS disturbances (mild drowsiness and sluggishness, increasing to giddiness with ataxia, coarse tremor, lack of co-ordination, dysarthria) and require withdrawal of treatment; with severe overdosage (serum concentrations above 2 mmol/litre), hyperreflexia and hyperextension of the limbs, convulsions, toxic psychoses, syncope, renal failure, circulatory failure, coma, occasionally death; goitre, raised antidiuretic hormone concentration, hypothyroidism, hypokalaemia, ECG changes, exacerbation of psoriasis and kidney changes may occur

Carbamazepine

Tablets , carbamazepine 100 mg, 200 mg

Uses:

prophylaxis of bipolar disorder unresponsive to or intolerant of lithium; epilepsy, trigeminal neuralgia (section 5.1)

Contraindications:

atrioventricular conduction abnormalities; history of bone-marrow depression; porphyria

Precautions:

hepatic impairment (Appendix 5); renal impairment (Appendix 4); cardiac disease (see also Contraindications); skin reactions (see Adverse effects); history of blood disorders (blood counts before and during treatment); glaucoma; pregnancy (Appendix 2 (neural tube screening)); breastfeeding (Appendix 3); avoid sudden withdrawal; **interactions:** Appendix 1

BLOOD, HEPATIC OR SKIN DISORDERS.	Patients or their carers should be told how to recognize signs of blood, liver or skin disorders, and advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, bruising or bleeding develop. Leukopenia which is severe, progressive and associated with clinical symptoms requires withdrawal (if necessary under cover of suitable alternative)
SKILLED TASKS.	May impair ability to perform skilled tasks, for example operating machinery, driving

Dosage:

Prophylaxis of bipolar disorder, *by mouth* , **ADULT** initially 400 mg daily in divided doses increased until symptoms are controlled to a maximum of 1.6 g daily; usual maintenance range 400–600 mg daily

Adverse effects:

dizziness, drowsiness, headache, ataxia, blurred vision, diplopia (may be associated with high plasma concentrations); gastrointestinal intolerance including nausea and vomiting, anorexia, abdominal pain, dry mouth, diarrhoea or constipation; commonly, mild transient generalized erythematous rash (withdraw if worsens or is accompanied by other symptoms); leukopenia and other blood disorders (including thrombocytopenia, agranulocytosis and aplastic anaemia); cholestatic jaundice, hepatitis, acute renal failure, Stevens-Johnson syndrome (erythema multiforme), toxic epidermal necrolysis, alopecia, thromboembolism, arthralgia, fever, proteinuria, lymph node enlargement, arrhythmias, heart block and heart failure, dyskinesias, paraesthesia, depression, impotence, male infertility, gynaecomastia, galactorrhoea, aggression, activation of psychosis, photosensitivity, pulmonary hypersensitivity, hyponatraemia, oedema, disturbances of bone metabolism with osteomalacia also reported; confusion and agitation in elderly

Sodium valproate

Enteric-coated tablets (Gastro-resistant tablets), sodium valproate 200 mg, 500 mg

Uses:

acute mania; epilepsy (section 5.1)

Contraindications:

active liver disease, family history of severe hepatic dysfunction; pancreatitis; porphyria

Precautions:

monitor liver function before and during therapy (Appendix 5), especially in patients at most risk (those with metabolic disorders, degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation); ensure no undue potential for bleeding before starting and before major surgery or anticoagulant therapy; renal impairment (Appendix 4); pregnancy (Appendix 2 (neural tube screening)); breastfeeding (Appendix 3); systemic lupus erythematosus; false-positive urine tests for ketones; avoid sudden withdrawal; **interactions:** Appendix 1

BLOOD OR HEPATIC DISORDERS. Patients or their carers should be told how to recognize signs of blood or liver disorders, and advised to seek immediate medical attention if symptoms including malaise, weakness, anorexia, lethargy, oedema, vomiting, abdominal pain, drowsiness, jaundice, or spontaneous bruising or bleeding develop

PANCREATITIS. Patients or their carers should be told how to recognize signs of pancreatitis and advised to seek immediate medical attention if symptoms such as abdominal pain, nausea and vomiting develop; discontinue sodium valproate if pancreatitis diagnosed

Dosage:

Acute mania, *by mouth* , **ADULT** initially 750 mg daily in divided doses, increased as quickly as possible to achieve the optimal response (maximum 60 mg/kg daily)

Adverse effects:

gastrointestinal irritation, nausea, increased appetite and weight gain, hyperammonaemia; ataxia, tremor; transient hair loss (regrowth may be curly); oedema, thrombocytopenia, inhibition of platelet aggregation; impaired hepatic function and rarely fatal hepatic failure (see Precautions—withdraw treatment immediately if malaise, weakness, lethargy, oedema, abdominal pain, vomiting, anorexia, jaundice, drowsiness); sedation reported and also increased alertness; behavioural disturbances; rarely pancreatitis (measure plasma amylase if acute abdominal pain), extrapyramidal symptoms, leukopenia, pancytopenia, red cell hypoplasia, fibrinogen reduction; irregular periods, amenorrhoea, gynaecomastia, hearing loss, Fanconi syndrome, dementia, toxic epidermal necrolysis, Stevens-Johnson syndrome (erythema multiforme), vasculitis, hirsutism, and acne reported

Drugs used in anxiety and sleep disorders

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.

Diazepam

Drug subject to international control under the Convention on Psychotropic Substances (1971)

Diazepam is a representative benzodiazepine anxiolytic and hypnotic. Various drugs can serve as alternatives

Tablets , diazepam 2 mg, 5 mg

Uses:

short-term treatment of anxiety and insomnia; status epilepticus, recurrent seizures; febrile convulsions, adjunct in acute alcohol withdrawal (section 5.1); premedication (section 1.3)

Contraindications:

respiratory depression; acute pulmonary insufficiency; sleep apnoea; severe hepatic impairment; myasthenia gravis

Precautions:

respiratory disease, muscle weakness, history of alcohol or drug abuse, marked personality disorder; pregnancy (Appendix 2); breastfeeding (Appendix 3); reduce dose in elderly or debilitated and in hepatic impairment (avoid if severe, Appendix 5), renal impairment (Appendix 4); avoid prolonged use and abrupt withdrawal; porphyria; **interactions:** Appendix 1

SKILLED May impair ability to perform skilled tasks, for example operating machinery,

TASKS. driving

Dosage:

Anxiety, *by mouth* , **ADULT** 2 mg 3 times daily increased if necessary to 15–30 mg daily in divided doses; **ELDERLY** (or debilitated) half adult dose

Insomnia, *by mouth* , **ADULT** 5–15 mg at bedtime

Adverse effects:

drowsiness and lightheadedness the next day; confusion and ataxia (especially in the elderly); amnesia; dependence; paradoxical increase in aggression; muscle weakness; occasionally headache, vertigo, salivation changes, gastrointestinal disturbances, visual disturbances, dysarthria, tremor, changes in libido, incontinence, urinary retention; blood disorders and jaundice; skin reactions; raised liver enzymes

Obsessive-compulsive disorders and panic attacks

Obsessive-compulsive disorders can be treated with a combination of pharmacological, behavioural and psychological treatments. Antidepressants such as **clomipramine** which inhibit reuptake of serotonin have been found to be effective. Panic attacks may be treated with behavioural or cognitive therapy. If this management fails, drug therapy may be tried. Some tricyclic antidepressants including clomipramine, or SSRIs can reduce frequency of attacks or prevent them completely. Benzodiazepines may be used in panic attacks resistant to antidepressants.

Clomipramine hydrochloride

Capsules , clomipramine hydrochloride 10 mg, 25 mg

Uses:

phobic and obsessional states; panic attacks

Contraindications:

recent myocardial infarction, arrhythmias (especially heart block); manic phase in bipolar disorders; severe liver disease; children; porphyria

Precautions:

cardiac disease (see Contraindications above), history of epilepsy; pregnancy (Appendix 2); breastfeeding (Appendix 3); elderly; hepatic impairment (Appendix 5); thyroid disease; phaeochromocytoma; history of mania, psychoses (may aggravate psychotic symptoms); angle-closure glaucoma, history of urinary retention; concurrent electroconvulsive therapy; avoid abrupt withdrawal; anaesthesia (increased risk of arrhythmias and hypotension); **interactions:** Appendix 1

SKILLED TASKS.	May impair ability to perform skilled tasks, for example operating machinery, driving

Dosage:

Phobic and obsessional states, *by mouth* , **ADULT** initially 25 mg daily, usually at bedtime (**ELDERLY** 10 mg daily) increased over 2 weeks to 100–150 mg daily; **CHILD** not usually recommended

Adverse effects:

sedation, dry mouth, blurred vision (disturbance of accommodation, increased intra-ocular pressure), constipation, nausea, difficulty in micturition; cardiovascular adverse effects particularly with high dosage including ECG changes, arrhythmias, postural hypotension, tachycardia, syncope; sweating, tremor, rash and hypersensitivity reactions (urticaria, photosensitivity); behavioural disturbances; hypomania or mania, confusion (particularly in elderly), interference with sexual function, blood sugar changes; increased appetite and weight gain (occasional weight loss); endocrine adverse effects such as testicular enlargement, gynaecomastia and galactorrhoea; convulsions, movement disorders and dyskinesias, fever, agranulocytosis, leukopenia, eosinophilia, purpura, thrombocytopenia, hyponatraemia (may be due to inappropriate antidiuretic hormone secretion); abnormal liver function test