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26.4.1 Psychopharmacology in medical practice 6465

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CONTENTS 26.4.1 Psychopharmacology in medical practice 6465 Philip J. Cowen 26.4.2 Psychological treatments 6470 Michael Sharpe and Simon Wessely 26.4.1 Psychopharmacology in medical practice Philip J. Cowen ESSENTIALS Drugs intended to treat psychiatric disorders are referred to as psy- chotropic drugs. The main categories are antidepressants, mood stabilizing drugs, antipsychotic drugs, and antianxiety drugs. These drugs are widely used in medical practice and most clin- icians are likely to have under their care several patients receiving treatment with them. Practitioners therefore need to have an under- standing of both the uses and unwanted effects of psychotropic drugs, and particularly of (1) their interactions with drugs used to treat other medical conditions, (2) characteristic abstinence syndromes that can occur with sudden discontinuation of antidepressants (par- ticularly selective serotonin reuptake inhibitors and venlafaxine) and anxiolytics. Introduction Psychotropic drugs are widely used in medical practice and most clinicians are likely to have under their care several patients re- ceiving treatment with this type of medication (Table 26.4.1.1). Most psychotropic drugs are prescribed for the treatment of depressive or anxiety disorders, reflecting the frequency of these conditions in both primary care and general hospital settings. Similarly, while the principal use of antipsychotic drugs is in the treatment of schizophrenia, such agents are also used in general hospitals in the management of the organic psychoses such as de- lirium and dementia. Finally, while treatment with mood

stabilizing drugs, such as lithium, is generally initiated by psychiatrists, patients receiving long-term treatment with these agents may require treat- ment for coexisting medical conditions, consequently knowledge of the effects of lithium on different body systems and its liability to produce adverse drug interactions will be required. For many psychiatric conditions, particularly anxiety and de- pressive disorders, psychological treatments are often as effective as psychotropic drugs and may have other advantages. Hence, if appro- priate psychological treatments are available, they should be con- sidered as an alternative to, or addition to, drug therapy. Special considerations Overdose Patients may present to medical services with the effects of delib- erate or accidental overdose of psychotropic drugs. Consequently, 26.4 Psychiatric treatments in the medically ill Table 26.4.1.1 Classification of clinical psychotropic drugs Name Examples of agents Indications Antipsychotic Haloperidol Quetiapine Risperidone Acute treatment of schizophrenia and mania, prophylaxis of schizophrenia Antidepressant Fluoxetine Venlafaxine Mirtazapine Major depression (acute treatment and prophylaxis), anxiety disorders, obsessive–compulsive disorder (SSRIs) Mood stabilizer Lithium Valproate Acute treatment of mania, prophylaxis of recurrent mood disorder Anxiolytic Diazepam Lorazepam Short-term relief of anxiety symptoms Hypnotic Temazepam Zopiclone Zolpidem Insomnia

section 26 Psychiatric and drug-related disorders 6466 when prescribing psychotropic drugs, particularly for depressed pa- tients, the risk of overdose should always be considered. If such a risk is present, the practitioner should: (1) ensure that medication is dispensed in small amounts; (2) consider asking a close relative to supervise the medication; (3) use a relatively nontoxic drug, if this is available. Pharmacokinetic factors Most psychotropic drugs are highly lipophilic and are well absorbed from the gastrointestinal tract. They are then metabolized by the liver to water-soluble derivatives that are in turn eliminated by the kidneys, hence the drug half-life will be prolonged in patients with hepatic or renal impairment and in older patients. When psycho- tropic medication is added to another drug treatment the possibility of drug interactions must be considered. For example, some se- lective serotonin reuptake inhibitors (SSRIs) are potent inhibitors of hepatic cytochrome P450 enzymes and can thereby increase plasma levels of drugs such as warfarin. Withdrawal of psychotropic medication Characteristic abstinence syndromes occur with sudden discon- tinuation of antidepressants (particularly SSRIs and venlafaxine) and anxiolytics. The main symptoms are: • Sleep disturbance—insomnia, nightmares • Mood symptoms—irritability, anxiety, emotional lability • Gastrointestinal symptoms—nausea, diarrhoea • Sensory—electric shock sensations, light-headedness, vertigo • Somatic—headache, lethargy, sweating The sudden discontinuation of lithium can provoke a ‘rebound’ mania in bipolar patients. It is therefore prudent to withdraw psy- chotropic drugs slowly whenever possible. It is also important to be able to distinguish withdrawal syndromes from a relapse of the dis- order being treated. Compliance and concordance with treatment Compliance with the prescribed drug regimen is an even greater problem with psychotropic drugs than it is in general therapeutics. Psychoactive drugs frequently have unpleasant side effects. These may be experienced early in treatment and before a therapeutic re- sponse is evident. Furthermore, patients may not see the need for treatment or believe that it can help them. Consequently, the suc- cessful and safe use of medication requires a collaborative relation- ship between patient and doctor. The term ‘concordance’ may be preferred to ‘compliance’, which carries the implicit assumption that the patient’s task is to obey instructions. It is therefore important to understand the patient’s view of their illness as well as of its treat- ment. Careful explanation of the likely benefits of treatment and what to expect, accompanied by written information, can help to ensure that the drugs you

prescribe are actually taken. Antidepressant drugs All antidepressant drugs in current use increase the activity of sero- tonin (5-hydroxytryptamine, 5-HT) and/or noradrenergic neurons in the central nervous system (CNS) through one mechanism or another. The pharmacological actions of both noradrenaline (norepinephrine) and 5-HT in the synapse are terminated by spe- cific reuptake pumps that draw these neurotransmitters back into the presynaptic nerve ending. Most antidepressants potentiate the action of 5-HT and noradrenaline by blocking this reuptake process. Selective serotonin reuptake inhibitors (SSRIs) The actions of SSRIs are confined to blockade of the reuptake of 5- hydroxytryptamine (5-HT) and their use is associated with a sus- tained increase in brain 5-HT neurotransmission. Most commonly used SSRIs These are citalopram, escitalopram, fluoxetine, paroxetine, and sertraline. Indications and use SSRIs are now first-line treatment for moderate to severe depres- sion. They are better tolerated than tricyclic antidepressants, less cardiotoxic, and are relatively safe in overdose. There are few im- portant therapeutic differences between them. If treatment is suc- cessful, it is usual to continue the antidepressant for at least 6 months (so-called continuation therapy). This reduces the risk of early relapse by about half. Some patients with recurrent depressive illness re- quire long-term ‘maintenance’ treatment with antidepressant drugs. Adverse effects The main adverse effects of SSRIs are shown in Table 26.4.1.2. SSRIs can cause activation and agitation early in treatment and there has been controversy as to whether this might be associated with an increased risk of suicidal behaviour. There is some evidence for this in young people and, with the exception of fluoxetine, SSRIs are contraindicated in the treatment of depression in patients less than 18 years old. The evidence for a pro-suicidal effect of SSRIs in adults is more equivocal; at a population level, some studies even show a decreased suicide rate correlating with SSRI prescription. However, it is likely that the initiation of antidepressant drug treat- ment of any kind is associated with some increased risk of self-harm Table 26.4.1.2 Newer antidepressants and their adverse effects Drug Mechanism Adverse effects SSRIs 5-HT reuptake blockade Nausea, insomnia, headache, anxiety, rash, sweating, sexual dysfunction, low sodium state, extrapyramidal movement disorders (rare), seizure (rare) Venlafaxine, duloxetine 5-HT and noradrenaline reuptake blockade Nausea, headache, insomnia, sweating, anxiety, hypertension, sexual dysfunction, seizure (rare), overdose toxicity (venlafaxine) Trazodone 5-HT2-receptor antagonism and α1-adrenoceptor blockade Sedation, dizziness, nausea, postural hypotension, priapism (rare), cardiac arrhythmias (rare), seizure (rare) Mirtazapine 5-HT2/α2-adrenoceptor agonist Sedation, weight gain, abnormal liver function tests, reversible agranulocytosis (rare), seizure (rare)

 in the first weeks of treatment. Depressed patients should there- fore be carefully monitored in the days after starting antidepressant medication and that medication should be prescribed in limited amounts. Drug interactions SSRIs, with the exception of citalopram and escitalopram, slow the metabolism of numerous other drugs including warfarin, theophyl- line, anticonvulsants, antipsychotics, and tricyclic antidepressants. Dangerous interactions, characterized by 5-HT neurotoxicity, have been reported between SSRIs and monoamine oxidase inhibi- tors. SSRIs may also produce 5-HT toxicity in combination with lithium, and with some medical drugs such as tramadol, linezolid, and triptans. SSRIs increase the risk of upper gastrointestinal bleeding, particularly if given in conjunction with nonsteroidal anti-inflammatory drugs (NSAIDs). Newer antidepressants Main drugs These can be classified as (a) selective serotonin-noradrenaline re- uptake inhibitors—duloxetine and venlafaxine; (b) monoamine re- ceptor antagonists—mirtazapine and trazodone. Venlafaxine is a potent blocker of 5-HT reuptake and at higher doses blocks the reuptake of noradrenaline as well. Duloxetine has

a similar action. Both trazodone and mirtazapine are 5-HT2 re- ceptor antagonists and block α1-adrenoceptors in addition, which gives them a sedating profile. Mirtazapine also blocks inhibitory presynaptic α2-adrenoceptors, resulting in an increased release of noradrenaline. Indications and use These antidepressants can be used to treat patients in whom SSRIs are poorly tolerated or found to be ineffective. With the exception of venlafaxine, these drugs lack significant cardiotoxicity and are rela- tively safe in overdose. Adverse effects The main adverse effects of the other, newer antidepressants are shown in Table 26.4.1.2. The major distinction between compounds is whether they are sedating. Drug interactions Duloxetine and venlafaxine, like SSRIs, potentiate 5-HT function and therefore can cause serious 5-HT neurotoxicity. Trazodone and mirtazapine may increase the sedative effects of other centrally acting drugs. Tricyclic antidepressants Tricyclic antidepressants (TCAs) inhibit the neuronal uptake of nor- adrenaline and 5-HT. They have numerous other pharmacological properties, which contribute to their adverse effects rather than their therapeutic activity. However, some of these adverse effects (e.g. sed-ation) can prove beneficial in certain circumstances. Main drugs These are amitriptyline, clomipramine, lofepramine, and nortriptyline. Indications and use Tricyclic antidepressants are now little used for the treatment of de- pression, but are still widely prescribed at relatively low doses as ad- juncts for the management of pain and insomnia. Adverse effects These are listed in Table 26.4.1.3. Drug interactions The ability of TCAs to block noradrenaline reuptake can lead to hypertension with systemically administered noradrenaline and adrenaline (epinephrine). Tricyclic antidepressants should not be used in conjunction with antiarrhythmic drugs, particularly amiodarone. Numerous other drugs including sodium valproate, calcium channel blockers, and SSRIs can increase the plasma levels of tricyclic antidepressants. Mood stabilizing drugs Lithium Lithium salts have inhibitory effects on receptor-transduction systems, particularly second messengers such as cAMP and phosphoinositol. The main uses of lithium are: • prophylaxis of recurrent mood disorders, especially manic de- pressive illness • acute treatment of mania • augmentation of antidepressant medication in patients with re- sistant depression Lithium remains a leading pharmacological treatment for the main- tenance phase of bipolar disorder. However, because of its potential toxicity and limited tolerability, anticonvulsant treatments and atyp- ical antipsychotic drugs are increasingly used for this purpose. The excretion of lithium from the body is critically dependent on the kidneys. Since there is little margin between therapeutic serum levels of lithium (0.5–0.8 mmol/litre) and those causing toxicity (>1.2 mmol/litre) clinical and laboratory assessment of renal func- tion should be done before starting treatment. Renal function tests

Table 26.4.1.3 Adverse effects of tricyclic antidepressants

Pharmacological action	Adverse effects
Muscarinic receptor blockade (anticholinergic)	Dry mouth, tachycardia, blurred vision, glaucoma, constipation, urinary retention, sexual dysfunction, cognitive impairment
α1-Adrenoceptor blockade	Drowsiness, postural hypotension, sexual dysfunction, cognitive impairment
Histamine H1 receptor blockade	Drowsiness, weight gain
Membrane stabilizing properties	Cardiac conduction defects, cardiac arrhythmias, epileptic seizures, overdose toxicity
Other	Rash, oedema, leucopenia, elevated liver enzymes

 should include urinalysis and measurement of plasma creatinine and electrolyte levels: care should be taken if there is any suggestion of impaired renal function (reduced estimated GFR (eGFR)). In the absence of clinical indications, it is usually sufficient to check lithium levels every three months and to repeat renal func- tion tests every six months. Lithium can also cause hypothyroidism, so thyroid function tests should be done prior to treatment and at six-monthly intervals thereafter. If necessary, thyroxine replacement

therapy can be added. Sudden withdrawal of lithium in patients with bipolar disorder can cause an acute rebound mania and should therefore be avoided if possible. Adverse effects The side effects of lithium are shown in Table 26.4.1.4. The most important are a result of the effect on the kidneys. Some degree of thirst and polyuria is common, and a few patients de- velop nephrogenic diabetes insipidus, probably caused by lithium blocking the effect of antidiuretic hormone on the renal tubule. Most patients taking lithium have a demonstrable impairment of tubular concentrating ability, although this is rarely of clinical sig- nificance. Glomerular function is less affected by lithium, but glom- erular damage and interstitial fibrosis have been reported following lithium toxicity. While long-term lithium treatment, even at thera- peutic plasma levels, can cause long-term renal impairment and renal failure, this risk can be minimized by maintaining the serum concentration within the therapeutic range. An increasing level of creatinine/decreasing level of eGFR (a fall of more than 4 ml/min per year, or to a value <30 ml/min) should prompt review by a renal physician. Drug interactions The narrow therapeutic index of lithium means that drug inter- actions that raise serum lithium levels can have serious clinical consequences. Important interactions can occur with diuretics, NSAIDs, ACE inhibitors, and angiotensin II receptor antagonists, all of which may increase lithium levels. Lithium levels may be in- creased by metronidazole and lowered by theophylline and antacids. While the effects of lithium on cardiac conduction are usually con- sidered benign, it may potentiate the effects of cardiac glycosides on conduction. Toxicity Acute lithium toxicity usually appears at a serum level above 1.2 mmol/litre. Early signs are coarse tremor, drowsiness, and dys- arthria. Higher plasma concentrations (>2.0 mmol/litre) can lead to seizures, coma, and death. Since lithium toxicity is potentially fatal, any suspicion of intoxication should lead to the immediate with- drawal of lithium treatment and close monitoring of serum lithium and plasma electrolyte and creatinine concentrations. Severely ill patients with high serum lithium levels may require dialysis. Sodium valproate Valproate is a simple branched-chain fatty acid with a mode of ac- tion that is unclear, although there is some evidence that it can slow the breakdown of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). This action could account for its anticonvulsant properties, but whether it also underlies the psychotropic effects is unclear. Indications and use Valproate is effective in the management of acute mania and in the longer-term prophylaxis of bipolar disorder. Valproate can be started at a dose of 200–400 mg daily, which may be increased once or twice weekly to between 1 and 2 g daily. Plasma levels of val- proate do not correlate well with either its anticonvulsant or mood stabilizing effects, but it has been suggested that efficacy in the treat- ment of mood disorders is usually apparent when plasma levels are above 50 µg/ml. Side effects Common side effects of valproate include gastrointestinal disturb- ances, tremor, sedation, weight gain, and transient hair loss. Serious side effects are rare, but fatal hepatic toxicity and acute pancreatitis can occur. Valproate may also cause thrombocytopenia and inhibit platelet aggregation, and increases in plasma ammonia can occur. Drug interactions Valproate potentiates the effects of central sedatives. It can in- crease the side effects of other anticonvulsants (without necessarily improving anticonvulsant control). It may increase plasma levels of phenytoin and TCAs. Other drugs Although not licensed for this indication in the United Kingdom, the anticonvulsant drug lamotrigine is increasingly used to treat depression in patients with bipolar disorder. Atypical anti- psychotic drugs such as quetiapine are also being used to treat bi- polar disorder. Antipsychotic drugs Antipsychotic drugs, also known as major tranquillizers or neuro- leptics, are a group of agents of varied structure used to treat schizophrenia and other psychoses. All antipsychotic agents have in common the ability to block dopamine receptors in the cen- tral nervous system, and it is likely that their antipsychotic effect is caused by blockade of dopamine D2 receptors in mesolimbic

Table 26.4.1.4 Adverse effects of lithium Central nervous system Drowsiness, lethargy, headache, memory impairment, fine tremor Cardiovascular system Conduction defects (rare) Gastrointestinal system Nausea, vomiting, diarrhoea Genitourinary system Polydipsia, polyuria, nephrogenic diabetes insipidus Endocrine system Hypothyroidism (T4 ↓ TSH ↑), hyperglycaemia, hyperparathyroidism Other Leucocytosis, skin rash, weight gain Signs of toxicity (plasma level: >1.2 mmol/litre) Nausea, vomiting, coarse tremor, drowsiness, dysarthria, seizures, coma, renal failure, cardiovascular collapse T4, thyroxine; TSH, thyroid stimulating hormone.

26.4.1 Psychopharmacology in medical practice 6469 regions of the brain. Blockade of D2 receptors in striatum explains the common occurrence of various kinds of extrapyramidal move- ment disorders. The newer so-called ‘atypical’ antipsychotic drugs have a varied pharmacology, but are less likely to produce extrapyramidal side effects at therapeutic doses than conventional agents such as halo- peridol. Some atypical agents such as amisulpride, are highly selective dopamine D2 receptor antagonists with selectivity for mesolimbic dopamine receptors. Others (e.g. risperidone, olanzapine, and quetiapine) have high affinities for the 5-HT2 receptor that exceed their affinities for the D2 receptor. Main drugs These are: (a) the conventional (typical) antipsychotic drugs— chlorpromazine, haloperidol, flupentixol, fluphenazine; (b) atyp- ical antipsychotic drugs—amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, and risperidone. Indications and use The main use of antipsychotic drugs is to treat schizophrenia. They are also used to treat mania and are sometimes given to depressed patients who have psychotic symptoms or who are particularly agi- tated. Some atypical antipsychotic drugs (for example, quetiapine and olanzapine) are helpful in the maintenance treatment of bipolar disorder and quetiapine has useful effects in the acute treatment of bipolar depression. Antipsychotic drugs are also used in the management of disturbed behaviour arising from other medical causes (e.g. confusional states), but their use as nonspecific tranquillizing agents should be short-term only because of their potentially ser- ious side effects. Some groups of demented patients (particularly those with Lewy body type dementia) can suffer severe extra- pyramidal effects from comparatively low doses of antipsychotic drugs. Patients with dementia also appear to be at increased risk of adverse cardiovascular events, particularly stroke, during anti- psychotic drug treatment. Antipsychotic drugs increase the risk of thromboembolic disease. Clozapine can be effective in up to 30% of patients with schizo- phrenia whose symptoms have not responded to other antipsychotic drugs (both typical and atypical). Notably it is effective in the treat- ment of both positive and negative symptoms of schizophrenia; the latter often responding poorly to other antipsychotic drugs. Adverse effects Abnormal movements Through their blockade of brain dopamine receptors, typical anti- psychotic drugs commonly produce a variety of extrapyramidal movement disorders that can mimic signs of basal ganglia disease, for example, acute dystonia and parkinsonism. The treatment of these movement disorders is by a reduction in dosage of the anti- psychotic drug or by the introduction of anticholinergic medica- tion such as benztropine. After a period of treatment, tardive (late onset) dyskinesia may develop. This consists of involuntary repeti- tive movements, usually involving the tongue and lips, though other parts of the body may be involved. Unfortunately, these movements are hard to treat and anticholinergic medication may make them worse. If possible, the antipsychotic drug should be stopped; this de- cision is often difficult because of the risk of relapse of the psychiatric disorder it is being used to treat. Atypical antipsychotic drugs are less likely to cause movement disorders including tardive dyskinesia. Weight gain Many antipsychotic drugs can cause weight gain; the risk is greatest with atypical agents, particularly clozapine, olanzapine, and quetiapine. These drugs are also associated with a greater risk of type 2 diabetes than conventional agents, as well as disturbances in lipid profile.

Patients taking atypical antipsychotics should therefore be monitored for weight gain and disturbances in glucose and lipid metabolism. Neuroleptic malignant syndrome Neuroleptic malignant syndrome is a rare but potentially very ser- ious reaction to antipsychotic drugs. It is characterized by fever, muscular rigidity, altered consciousness, tachycardia, and labile blood pressure. Abnormal investigations include leucocytosis and markedly raised creatinine phosphokinase. Management is by im- mediate withdrawal of the antipsychotic drug. The drugs bromo- criptine and dantrolene may be helpful. If there are cardiovascular, respiratory, and renal complications, ICU support may be required. The most common adverse effects of atypical antipsychotic drugs are shown in Table 26.4.1.5. Drug interactions Antipsychotic drugs potentiate the effects of other central sedatives. They may delay the hepatic metabolism of TCAs and antiepileptic drugs, leading to increased plasma levels of these agents. Clozapine Table 26.4.1.5 Adverse effects of atypical antipsychotic drugs Drug EPS Prolactin Weight gain Adverse effects Amisulpiride + ↑ + Insomnia, agitation, nausea, constipation, QT prolongation (rare) Clozapine 0 0 +++ Agranulocytosis—regular white cell monitoring mandatory, myocarditis and myopathy (rare), fatigue, drowsiness, hypersalivation, sweating, tachycardia, postural hypotension, nausea, constipation, ileus, urinary retention, diabetes Olanzapine +/0 0 +++ Somnolence, dizziness, oedema, hypotension, dry mouth, constipation, diabetes Quetiapine 0 0 ++ Somnolence, dizziness, postural hypotension, dry mouth, abnormal liver function tests, QT prolongation, diabetes Risperidone + ↑ + Insomnia, agitation, anxiety, headache, impaired concentration, nausea, abdominal pain 0, not present; +, sometimes; ++, often; +++, can be excessive; EPS, extrapyramidal symptoms.

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