Chapter 35: Basic Principles of Psychopharmacology

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The introduction of lithium (1948), antipsychotics (chlorpromazine - 1952), antidepressants (imipramine - 1957), and benzodiazepines (chlordiazepoxide - 1960) heralded a dramatic change in the fate of people with severe mental illness. Prior to the discovery of these treatments, the mainstay of management was in essence removal from society and containment in asylums - with little reprieve from the severe symptoms themselves, although, with time some may have spontaneously remitted from their illness. Only a few sedative medications were in use, such as paraldehyde, barbiturates and morphine to provide some relief. However, they had no effect upon the course of the illness. The only biological treatments available were electroconvulsive therapy and psychosurgery, both widely used and administered beyond their present-day indications because of the paucity of alternatives. The widespread uptake of the new psychopharmacological treatments led to a dramatic fall in the population of people housed in asylums and contributed to the emergence of de-institutionalisation. Today, two of the top 10 prescribed drugs by volume in Australia are antidepressants (Editor, 2023).

Although there is a neuroscience-based nomenclature available for defining the class of action of psychotropic medications (**https://nbn2r.com/**) this is rarely used in practice. We will describe the medications by their principal action, although their use in practice goes beyond that. Psychotropic medications have specific actions, for example, the antipsychotics block post-synaptic dopamine

receptors or selective serotonin receptor inhibitors increase serotonin availability by limiting its reuptake into the presynaptic cell. These actions suggest neurotransmitter hypotheses that provide simplistic and incomplete explanations for how medications work. Psychotropic medications all influence many different neurotransmitters (they are 'dirty' drugs) but also other pathways such as immunological systems. Their actions are complex and are not fully understood.

A Reminder of the Importance of Pharmacokinetics

All medications achieve a clinical effect by balancing several factors. Firstly, the medication must have an affinity for the pharmacological site of action that is deemed to be therapeutic. In other words, does it act at the receptors which are important for the action on the disease? An example of this is the degree of binding of antipsychotic medications to the dopamine D_2 receptor. Secondly, the drug needs to be able to reach a suitable concentration at the site of action within the brain – its bioavailability needs to be such that it will engage target receptors. An example of this critical first step is the low bioavailability of the antipsychotic asenapine if administered orally because of its high first-pass metabolism. In this case not enough of the medication reaches the brain. Then the half-life of the medication, as determined by its metabolism and excretion, needs to allow the medication to reach a concentration that can sustain an action. Some medications such as quetiapine or venlafaxine are usually administered in extended-release compounds because of the rapid metabolism of the compound. And finally, individual factors such as age, genetics and preexisting renal or hepatic impairment need to be taken account of when assessing the risks as against benefits of the medication, such as the need to be very careful in the monitoring of lithium in the presence of renal impairment (see Figure 35.1)

Clinical response	=	Affinity for and intrinsic activity at the sight of action (pharmacodynamics)	X	Drug concentration at site of action (pharmacokinetics (MADE) • **M**etabolism • **A**bsorption • **D**istribution • **E**limination	X	Underlying biology of patient (AGED) • **A**ge • **G**enetics • **E**nvironment • **D**isease

Figure 35.1. Factors that contribute to the achievement of a clinical response. Adapted from Preskorn (2012).

Antipsychotics

Chlorpromazine, the first of the antipsychotics, was first synthesised in 1950 and was immediately noted to cause detachment and calm in patients in surgical and psychiatric settings. Jean Delay and Pierre Deniker in 1952 were some of the first psychiatrists to trial the medication and they reported that it was of benefit in controlling manic and psychotic agitation. Within a year it was widely available for use in psychiatry throughout France (Seeman, 2021). The discovery that drugs that block dopamine transmission (D_2 receptor) have an antipsychotic effect led to the development of the dopamine hypothesis for schizophrenia (Seeman, 2021).

Table 35.1. Antipsychotic Medication

Class	**Commonly used medications available in Australia**	**Major indications and application in clinical practice**
First generation antipsychotics (typical)	*Chlorpromazine, flupentixol, haloperidol, zuclopenthixol*	Schizophrenia Mania Psychosis
Second generation antipsychotics (atypical antipsychotics)	*amisulpride, asenapine, clozapine, lurasidone, olanzapine, paliperidone quetiapine, risperidone, ziprasidone*	Schizophrenia Psychosis Mania As adjunctive treatment for MDD Bipolar depression
Third generation antipsychotics	*aripiprazole, brexpiprazole, cariprazine*	Schizophrenia Psychosis Mania As adjunctive treatment for MDD Bipolar depression

Note: MDD = Major Depressive Disorder

The 'first generation' antipsychotic medications all have a common action in blocking the D_2 receptor in the mesolimbic and mesocortical system. There are other dopaminergic pathways in the brain, and blocking dopamine in these areas leads to adverse effects including extrapyramidal symptoms (EPS) due to dopamine blockade in the nigrostriatal system and increased prolactin release due to dopamine blockade in the tuberoinfundibular system. In the 1990s a second generation of antipsychotics became available. These antipsychotics, based on the

action of clozapine, also acted on the $5HT_{2A}$ serotonin receptors (along with other receptors) which reduced the risk of EPS. More recently a third generation of antipsychotic medications which act as partial agonists at the dopamine $D_{2/3}$ receptors have been introduced. Notably, there has been little advance in terms of efficacy, between the first and most recent generation antipsychotics. The difference between the various agents lies predominantly with their tolerability and adverse effect profiles. Table 35.1 shows an overview of antipsychotic medications and Table 35.2 lists the typical side-effects these medications may cause.

Table 35.2. Propensity for adverse effects from antipsychotic medication

Class	Sedation	Weight	EPS	Chol	Prolactin	QTc
1st Generation Antipsychotics						
chlorpromazine	+++	+++	++	+++	+++	++
haloperidol	+	++	+++	+	+++	++
zuclopenthixol	+++	++	++	++	+++	-
2nd generation - D_2 & $5HT_2$ antagonists						
asenapine	++	++	+	-	+	+
clozapine	++++	+++	-	XXX	-	+
lurasidone	++	+	+	-	+	-
olanzapine	+++	+++	-	++	+	+
paliperidone	+	++	+	-	+++	+
quetiapine	++	++	+	-	+	++
risperidone	+	++	++	-	+++	+
ziprasidone	+	+/-	+	-	-	++
D_2 & D_3 antagonist						
amisulpride	+	+	++	-	+++	++
3rd Generation – D_2 or D_2/D_3 partial agonists						
aripiprazole	+	+	-	-	-	-
brexpiprazole	+	+	-	-	-	-
cariprazine	+	+	++	-	-	-

Note: - = no effect; +mild; ++ = moderate; +++ = large effect; XXX – highly anticholinergic, paradoxical increase salivation. EPS = Extrapyramidal Side Effects, Chol = anticholinergic effect, prolactin = increased prolactin secretion, QTc = prolongation of QTc interval. (Galletly et al., 2016)

Antipsychotic medication can be administered as oral, sublingual or intramuscular preparations. Intramuscular preparations can aim for short term effect (e.g. zuclopenthixol acetate) or as long acting injectables (LAI), sometimes known as "depot" medications, which aim to improve treatment adherence over

the longer term. These preparations can be given from every 2 weeks to up to 6-monthly.

Antidepressant Medications

The introduction of imipramine, a tricyclic antidepressant (TCA) and the monoamine oxidase inhibitors (MAOIs) led to a dramatic change in the treatment of severe depression. Prior to this, the only effective treatment for severe depression were ECT and for some psychosurgery. Psychotherapy had limited success for most severe forms of depression and in particular melancholia – largely because patients were too unwell to engage in meaningful therapy. A monoamine hypothesis of depression was formulated in response to these initial discoveries in the same way that the simplistic dopamine hypothesis of schizophrenia was developed after the introduction of antipsychotics (Hirschfeld, 2000).

The first generation of antidepressants, the tricyclics and MAOIs, while effective as antidepressants were limited by their significant adverse effect burden and toxicity at high doses, which made them dangerous in both intentional and inadvertent overdosing. The tricyclics caused anticholinergic adverse effects (dry mouth, blurred vision, postural hypotension, urinary retention [for males] and worsening of glaucoma) and the MAOIs required patients to be on a low tyramine diet to avoid the risk of a hypertensive crisis. These were significant limitations. The introduction of drugs that targeted serotonin – namely, Selective Serotonin Reuptake Inhibitors (SSRIs) in the 1990s, with fluoxetine (Prozac), completely changed this.

The SSRIs were easier to prescribe than the TCAs, as they had fewer adverse effects and were safer in overdose. This quickly led to an upsurge in prescribing antidepressant medications to a broader population. At the same time, and akin to existing antidepressants, the SSRIs were found to be effective in the treatment of anxiety disorders. Anxiety and depression are frequently seen together and changes in the serotonergic system are common to both (Pourhamzeh et al., 2022). However, neither set of disorders should be seen simply as a disease of the serotonergic system, rather a far more complex process extending beyond this single neurotransmitter system is thought to be responsible (see chapter 25). Table 35.3 shows an overview of antidepressant medication.

Table 35.3. Antidepressant Medications.

Class	Commonly used medications available in Australia	Major indications
Tricyclic antidepressants (TCA)	*amitriptyline, clomipramine, dosulepin, imipramine, nortriptyline*	MDD Anxiety disorders OCD (clomipramine only) Pain
Noradrenergic and specific serotonergic antidepressant (NaSSA)	*mirtazapine*	MDD
Selective Serotonin Reuptake Inhibitors (SSRIs)	*citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline,*	MDD Anxiety disorders OCD
Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs)	*venlafaxine, desvenlafaxine, duloxetine*	MDD Anxiety disorders OCD
Monoamine oxidase Inhibitors (MAOI)	*phenelzine, tranylcypromine,*	MDD Atypical depression Anxiety disorders
Reversible inhibiter of monoamine oxidase (RIMA)	*moclobemide*	MDD
Noradrenaline reuptake inhibitor	*reboxetine*	MDD
Selective catecholamine (Noradrenaline & Dopamine) reuptake inhibitor	*bupropion*	MDD Smoking cessation
Serotonin Modulator	*vortioxetine*	MDD
Melatoninergic	*agomelatine*	MDD Generalised anxiety disorder

Note: MDD = Major Depressive Disorder, OCD = Obsessive Compulsive Disorder

Anxiolytics, Hypnotics and Sedatives

Relieving anxiety, calming fears or helping to induce sleep have long been important aims for medicine or traditional health care from earliest times, and substances used to achieve this have included alcohol, cannabis, kava, opioids and many other herbal agents. Treatments for anxiety and insomnia were some of the earliest psychoactive substances synthesised and included bromide salts, chloral hydrate paraldehyde and barbiturates. In the 20th century, the barbiturates were widely used, both as sleeping pills and antianxiety agents. However, there were significant problems with them, particularly the high risk of dependence and their lethality in overdose.

The introduction of the benzodiazepines (initially chlordiazepoxide) was a considerable advance as they were safe in overdose as compared to antidepressants and yet highly effective in reducing anxiety and calming individuals. At the time the potential for drug dependence was not known but this became a significant problem as well the experience of severe withdrawal symptoms upon cessation. Dependence caused patients to seek prescribers 'doctor shopping' as prescribing became restricted. This is particularly a risk in benzodiazepines with a short half-life, such as alprazolam, which has led to their use being restricted. While they were originally first line treatments for anxiety disorders, this role has been superseded by the SSRIs.

Benzodiazepines are also commonly used as sedatives or hypnotics. Again, due to the risk of dependence the use of these medications for insomnia is not recommended beyond the short term. Finally, a benzodiazepine such as midazolam, which can be used parenterally, has become invaluable for the short-term management of patients who are highly agitated in emergency situations. Diazepam, clonazepam and lorazepam may also be used parenterally. Table 35.3 shows an overview of anxiolytics, and hypnotics and sedatives.

Benzodiazepines, zopiclone and barbiturates, along with many anaesthetic agents and anticonvulsants, all act as allostatic modulators of the GABA-A receptors, increasing GABAergic activity and contributing to tonic inhibition across the brain (Koh et al., 2023; Kim et al., 2020).

Table 35.4. Anxiolytics, Hypnotics and Sedatives

Medication type	Class	Commonly used medications available in Australia	Major indications
Anxiolytics	Anxiolytics	*alprazolam, bromazepam, clobazam, clonazepam, diazepam, lorazepam, oxazepam*	Anxiety, alcohol withdrawal, catatonia, epilepsy, muscle spasm, panic attack
Hypnotics and sedatives	Benzodiazepine hypnotics	*flunitrazepam, midazolam, nitrazepam, temazepam,*	Anaesthesia, insomnia
	Benzodiazepine related hypnotics	*zopiclone*	Insomnia

Lithium and Anticonvulsant Drugs

Lithium, a simple salt, was found to have marked antimanic properties by the Australian psychiatrist John Cade, making it one of the most specifically targeted medication we have in psychiatry (see also; Finding Sanity by Greg De Moore and Ann Westmore, Allen and Unwin, 2016) (Malhi et al., 2024). It is thought to achieve this by acting upon multiple steps of intracellular signalling and other cellular processes in a highly complex web of activity promoting neuroprotection and neural plasticity (Alda, 2015).

Lithium transformed the management of manic-depressive illness - the earlier term for bipolar disorder and led the pharmacological era in psychiatry It was found to have a prophylactic mood stabilizing effect, that prevented bipolar relapses to either pole of the illness. It is also used as an augmenting agent in major depressive disorder. Lithium is a simple molecule that is excreted in the urine unmetabolized – however it has a therapeutic window, which needs to be maintained to achieve efficacy and avoid both acute and long-term adverse effects such as thirst, tremor, thyroid changes, renal dysfunction and gastrointestinal effects. Details regarding the therapeutic range and monitoring can be found in the RANZCP Clinical Practice Guidelines for Mood Disorders (Malhi et al., 2016)

Certain anticonvulsants have also been found to have mood stabilizing effects, including carbamazepine, sodium valproate and lamotrigine. These medications were heavily marketed by the pharmaceutical industry for use in bipolar disorder. This contributed to lithium falling out of fashion, despite being the most effective mood stabilizer and antimanic agent. These anticonvulsants are also considered to be mood stabilizers (as are the second-generation antipsychotics), but they don't have the unique properties lithium has. Sodium valproate is contraindicated for women of childbearing age as it has teratogenic effects and can lead to infants born with intellectual impairment. It is also not recommended for males who are planning to father, as their offspring are at increased risk of neurodevelopmental disorders too. Table 35.5 shows an overview of mood stabilizers.

Table 35.5. Mood stabilizers.

Class	Commonly used medications available in Australia	Major indications
	Lithium[1]	Bipolar disorder, adjunctive treatment for MDD
Anticonvulsant mood stabilizers	*Carbamazepine, Lamotrigine, Sodium valproate,*	Bipolar disorder, epilepsy

[1] Lithium is the only mood stabilizer that has the only long-term prophylactic effect and has genuine effect on both poles of the disorder.

Stimulant Medications

Stimulants are primarily prescribed for the treatment of attention deficit hyperactivity disorder (ADHD). They are also used for the treatment of sleep disorders such as narcolepsy, binge eating disorder and treatment resistant depression. Due to the risk of misuse and diversion the supply of these medications has additional restrictions. There has been a doubling in the prescription of stimulants since 2018 in Australia (Australian Institute of Health and Welfare, 2024). This has paralleled an increased awareness of ADHD and demand for stimulants. A careful approach to the assessment and diagnosis of people with ADHD along with the consideration of behavioural and family treatments is recommended (see Chapter 25) Table 35.6 shows an overview of stimulants.

Table 35.6. Stimulants.

Class	Commonly used medications available in Australia	Major indications
Stimulants	Armodafinil, dexamfetamine, lisdexamfetamine, methylphenidate, modafinil	ADHD Narcolepsy Binge eating disorder
Non-stimulant medication	Atomoxetine, guanfacine	ADHD

Key Principals

A number of considerations need to be thought through when prescribing psychotropic medication - we want to prescribe a medication that is effective, well tolerated and safe.

Make a Diagnosis

First, there needs to be a clear diagnosis of the patient's disorder. This does not negate the importance of a biopsychosocial and lifestyle formulation, which will guide the comprehensive management of the patient. The diagnosis (along with the presenting symptoms) guides the clinician as to which medication is appropriate for the patient, if indeed medication is necessary. Non-pharmacological options should always be considered and, even if medication is prescribed, non-pharmacological and psychosocial options should also be used.

Patient Preference

A key consideration in selecting a medication is patient preference. Poor adherence to medication is frequent in mental health with up to 44-56% of people with a severe mental illness being non-adherent (Semahegn et al., 2020). This makes poor treatment adherence one of the commonest reasons why treatment with medication fails. Adherence is improved if the patient is involved in the decision about which treatment to take and this is best done in a shared decision-making model (Hoffmann et al., 2014). This includes a discussion about the expected benefits and potential adverse effects of the medication. Be aware that patients might have misinformation, from the internet or through word of mouth, about the adverse effects of medications. In such situations, it is essential to listen to the patient's concerns and present them with clear and accurate information

about the drug, including providing them with consumer fact sheets. Personal, familial and cultural factors need to be taken account of.

A discussion of the risks and benefits of a medication, taking into account patient preference, is an essential part of prescribing and part of the process of obtaining consent from the patient. Even though in psychiatry people can be compelled under the Mental Health Act to take a particular medication, their concerns, especially about adverse effects, need to be considered.

Treatment adherence can be improved by a wide range of evidence-based interventions. This includes simplifying when medication is taken, making this only once in the 24-hour cycle, preferably at night as many psychotropic medications can be sedating; or how it is dispensed, multiple medications can be pre-packaged by the pharmacist. Using prompts such as an alert in the person's mobile phone or leaving the medication next to the toothbrush that is used every night can be effective as can finding other ways of including taking medication in the regular routine of going to bed. Enrolling the patient in a formal program for treatment adherence can be useful. These programs have education, community support and automatic prompts to remind patients to refill prescriptions. They often involve the pharmacist more actively in the patient's care. Cognitive behavioural therapy programs have been developed specifically to improve adherence. Some antipsychotic medication can be given as a long-acting injectable preparation. Sometimes this route of administration is the patient's choice. When medication compliance will be a problem, long-acting injectable antipsychotic medication may need to be mandated as part of a community treatment order under the Mental Health Act. Finally, electronic medication monitoring systems that can check on actions such as opening a pill bottle, are being used in pharmacological trials and increasingly, will be available for general community use (Kini and Ho, 2018). Despite all these interventions, the basic task of explaining why someone should take a medication remains an essential part of the role of a doctor.

Efficacy

When we prescribe a medication for a patient, we need to ensure that the medication is effective in treating the patient's principal diagnosis or symptoms profile. All psychotropic drugs will have been tested in randomised controlled trials to test their efficacy compared with placebo, the gold standard clinical trial. All medications must have demonstrated efficacy in pivotal clinical trials before they are approved for use for a particular indication, and before they can be prescribed. In Australia, such approval comes from the Therapeutic Goods Administration (TGA) so they can be listed on the Pharmaceutical Benefits Scheme (PBS).

In trying to determine the efficacy of a particular treatment we need to look at individual randomised controlled trials (RCTs) and the systematic reviews and meta-analyses performed when RCTs are brought together. These will provide the best sources of evidence for the efficacy of a medication. A recent development has been to compare the efficacy of drugs using network meta-analyses, that allow comparison between various drugs being used to treat a particular condition. Generally, drugs are not tested against each other in clinical trials, but they will all have been compared to placebo; in a network meta-analysis it is possible to extrapolate the comparative efficacy by examining how each drug compares with placebo.

A problem with RCTs is that the participants are generally not typical of the patients seen in routine clinical practice. Participants are recruited based on having a straightforward diagnosis, with no comorbidities, no underlying personality disorder, no physical health problems and being reliable in taking medication. Women of childbearing age, unless they are on contraception, children or adolescents and the elderly are excluded from efficacy studies. By contrast, large scale effectiveness studies recruit 'real world' patients with fewer exclusion criteria and provide better evidence of the effectiveness of psychotropic medication. However, there are too few such studies.

Psychotropic medications also have a range actions that are not addressed by the general categories of "antidepressant" and "antipsychotic" (Moncrieff and Cohen, 2009), for example antipsychotics have been used in the treatment of depression. While there are arguments about how the medications work, the key consideration is how effective the drug is in the treatment of a particular disorder or symptom.

Tolerability

An effective medication is not going to benefit a patient if it is not taken as prescribed. Poor tolerability is one of the main reasons patients do not take their medication. All medications have some side-effects (or adverse effects), of varying degrees of severity. These adverse effects arise in part because of the pharmacodynamics of the drug (or what the drug does to the body). Psychotropic drugs have effects beyond their primary targeted action, with many different neurotransmitter systems affected which contribute to the adverse effects. For example, the therapeutic effect of the first-generation antipsychotics is through dopaminergic blockade in the mesolimbic system, but these same medications also block dopamine in the nigrostriatal system causing extrapyramidal symptoms and

in the tuberoinfundibular system leading to prolactin release causing gynaecomastia and sexual side-effects.

Antidepressants have a range of different adverse effects and in determining the most appropriate medication for the patient there needs to be a discussion with the patient about the side-effects the patient does not want to potentially have, as shown in Figure 35.2.

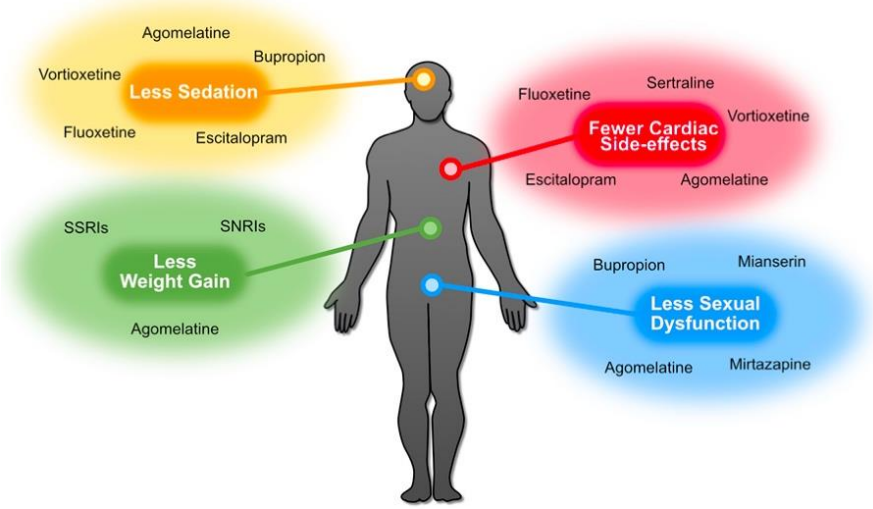

Figure 35.2. Adverse effect profiles of the antidepressants. Adapted from Malhi et al. (2021).

How the drug is dealt with by the body, its absorption, distribution, metabolism and excretion (pharmacokinetics) influence serum levels of the active drug and will also contribute to the development of adverse effects. The pharmacokinetics of the drug, such as their propensity to induce or inhibit the cytochrome system (CYP450 enzymes) can also contribute to interactions with other medications the patient may be taking. Adverse effects can arise as well from psychological factors, what the patient expects the medication to do. It is noteworthy that in RCTs, patients randomised to placebo will generally report some adverse effects (a nocebo effect).

How to Use Medications

Clinical Practice Guidelines, such as those developed for the Royal Australian and New Zealand College of Psychiatrists (RANZCP), bring together

the various clinical trials and meta-analyses to provide guidance on the most efficacious medications to be used for the major psychiatric disorders. The RANZCP has produced guidelines for the Anxiety disorders, Mood disorders, Schizophrenia and Eating disorders (**https://www.ranzcp.org/clinical-guidelines-publications**). Guidelines produced by the National Institute for Health and Care Excellence (NICE) in the UK (**https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-guidelines**) complement and extend College guidelines across a far broader range of disorders. Practical information about indications, dose and adverse effects is available through eTherapeutic Guidelines (Judd et al., 2021) or the Maudsley Prescribing Guidelines in Psychiatry (Taylor et al., 2021). Both resources are available online.

Conclusion

The number of medications available for treatment of psychiatric disorders has grown steadily over the past three decades and effectiveness and evidence base for these treatments is now comparable to other areas of medicine (Leucht et al., 2012). Their use in clinical practice is enhanced by the wide range of psychological interventions that are sometimes as effective or even more so for some psychiatric conditions – such as anxiety disorders (Huhn et al., 2014). As clinicians, we need to have a working knowledge on the pharmacodynamics, pharmacokinetics and adverse effects of the medications to allow us to communicate to our patients why we are suggesting they take a particular medication. This will allow you to give the best advice for your patients as well as being able to anticipate any adverse effects. Finally, medications only have an effect if they are taken, and working with your patient to establish the best course of treatment is essential.

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Cite as:

Boyce, P., Harris, A. (2024). Basic principles of psychopharmacology. In Boyce, P., Harris, A., and Malhi, G.S. (Eds.), *The Sydney textbook of psychiatry* (pp. 531–544). The University of Sydney.

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