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HANDBOOK OF PSYCHIATRIC MEDICATION

Introductory Overview • Treatment Approaches

VOLUME 2

Foreword

There is general agreement on the value of evidence-based medicine in general practice. And there is growing acknowledgement that the treatment of psychiatric disorders is an important component of primary care. This volume addresses the logical conclusion from these two premises; there is a need for an evidence-based approach to the use of psychiatric medications in general practice.

While the evidence base of psychopharmacology grows annually, there are relatively few attempts to synthesise this literature for general practitioners. Lengthy and cumbersome guidelines are unlikely to be read, much less implemented. Our aim here was to synthesise the evidence in a readable and easy-to-use format, using pharmacotherapy algorithms. The current volume updates previous attempts to meet this aim.[1]

The approach here draws in part on our experience with Continuing Medical Education courses for general practitioners. To that extent, we are grateful to the many GPs who have attended these courses, and who have advised us on how to improve them. We are also grateful to our colleagues who have helped us with this teaching, and to those in the pharmaceutical industry who have supported such teaching over the years.

It would perhaps be remiss if we did not end by emphasising that psychiatry is concerned not only about brain circuitry and neurotransmitters, but also about the patient-doctor relationship, and the broader intersections between society and the individual. Arguably, psychopharmacology is both a science and a humanity.[2] We hope that the treatment algorithms provided here are implemented with good clinical judgement.

Prof Dan J Stein

REFERENCES

1. Stein DJ, Seedat S, Niehaus DJH, Pienaar WP, Emsley RA: Psychiatric Medications in Primary Care: Algorithms and Guidelines. University of Stellenbosch, Cape Town; 1998-2004.
2. Stein DJ: The Philosophy of Psychopharmacology: Happy Pills, Smart Pills, Pep Pills. Cambridge University Press, Cambridge; 2008.

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Information for Prescribers

When prescribing any product listed in *MIMS Handbook of Psychiatric Medication,* doctors should be mindful of the important points listed below.

- Hypersensitivity to the ingredient(s)/components of any medicine contra-indicates its use.
- Medicines should not be prescribed to pregnant or lactating women unless the anticipated benefit clearly outweighs any potential risk to the foetus.
- The possibility of drug accumulation should be considered in the presence of significant renal or hepatic impairment.
- Tolerance to medicines is likely to be less with extremes of age.
- Side effects refer only to those which occur at the recommended dosages and correct route of administration.
- Drug interferences with laboratory tests and physical incompatibilities common with parenteral solutions have not been included.
- For additional information on dosage directions, particularly in the case of parenteral products, consult the *MIMS Desk Reference* – where applicable, the pharmaceutical company or the current package insert.
- Mono-amine oxidase inhibitors (MAOIs) have a prolonged action so patients should not take any of the foods or medicines known to cause reactions for at least 14 days after stopping treatment.
- Certain medicines (ie, those that cause CNS depression) may lead to drowsiness and impaired concentration, which may be aggravated by the simultaneous intake of alcohol or depression agents.

1: Principles of Prescribing Psychiatric Medications

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To begin at the beginning, it is worthwhile discussing some principles of prescribing psychiatric medications.

TREATMENT BEGINS WITH DIAGNOSIS

Psychiatric diagnosis has made important advances during the past few decades. *The Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) and the International Classification of Disease (ICD-11), for example, provide diagnostic criteria and guidelines that allow for the reliable diagnosis of different psychiatric disorders.[1] Obtaining a full history from both the patient, as well as from significant others, and other treating professionals, is paramount. Different psychiatric disorders and their subtypes are treated with different medications; thus, successful treatment depends on accurate diagnosis and assessment.

Research suggests that the most critical error made by primary care practitioners working with psychiatric disorders is failing to recognise these conditions.[2] Of course, it is also essential to recognise the existence of substance-use disorders and underlying general medical conditions that may lead to psychiatric symptoms. Chapter 2 of this handbook provides clinicians with the basics of the DSM-5 and ICD-11 approaches and each chapter of this handbook provides ICD-11 diagnostic guidelines for the disorders under discussion.

IDENTIFY SPECIFIC TARGET SYMPTOMS

Once a diagnosis is made, specific symptoms should be identified as targets for change during medication treatment. Such symptoms may be those that are central to the disorder (e.g., feeling "down" in depression), those that are distressing to the patient (e.g., loss of libido during a depression), or those that cause functional impairment (e.g., loss of concentration during depression).

Response of both objective disability and subjective wellbeing (quality of life) should be determined during pharmacotherapy. Although there are some controversies in the literature about the value of routine screening for psychiatric disorders such as depression[3-5], there is growing evidence of the value of measurement-based care, which employs standardised symptom-severity scales to monitor progress.[6]

Several rating scales are included in this volume for the convenience of clinicians. These provide validated assessments for both the patient and the clinician of the extent to which a medication is successful in reducing symptoms of any particular diagnosis. There is increasing emphasis on the importance of aiming for symptom remission and functional recovery, rather than merely symptom reduction.[7]

PSYCHO-EDUCATION MUST PRECEDE TREATMENT

Ignorance about psychiatric disorders is rife. These conditions continue to be viewed with great suspicion and stigma, which may serve as significant barriers to treatment.[8] It is helpful for clinicians to ask patients to describe their understanding of the underlying causes and best treatments of their psychiatric symptoms.[9] All too often, lay explanations of disorders centre on "weakness of will" and treatment involves "stress reduction". Psychiatric medication is often thought to be a "crutch", "addictive", or "unnatural".

Clinicians need to present a different model: Psychiatric disorders are medical conditions.[10] And like other medical disorders, they may involve a complex interplay of nature and nurture, but "weakness of will" is more likely a symptom of depression than a cause of psychiatric symptoms. Psychiatric medication acts at particular brain receptors which are made for endogenous ligands; they are therefore some of the most "natural" of compounds. Most are non-addictive, and they are as much a "crutch" as is insulin for the person with diabetes.

Not all patients will agree with this model, in which case a shared treatment model will need to be negotiated. There is growing and valuable literature on shared decision-making.[11-13] This is relevant to treatment initiation and treatment discontinuation; people often have understandable reservations about taking medication once they are feeling better.[14,15] In many psychiatric disorders, this unfortunately results in relapse. Rather than referring to "compliance", we should perhaps focus on "concordance", emphasising negotiated agreement. This leads to the next subject; the patient as a person.

REMEMBER THE PERSON

Any medical intervention should be made with the person in mind. A focus on target symptoms and side effects should not detract from understanding the patient's current circumstances, the meaning that is being made of treatment, and the relationship with the doctor. The efficacy of medication has at times been exaggerated.[16] Conversely, psychotherapy has an essential role in the treatment of psychiatric disorders.[17-19]

Cognitive-behavioural psychotherapy, for example, is effective in the treatment of mild to moderate depression, in the treatment of anxiety disorders, and as an adjunct in treatment-resistant conditions.[17,18,20] Indeed, evidence suggests that cognitive-behavioural treatment has a longer-lasting positive effect than medication in the treatment of some anxiety disorders.[21] Working with the patient's family is often crucial, both in making sure that cognitive-behavioural techniques are actually used, and in disorders (such as substance abuse and personality disorder) where structure and limit-setting are important parts of the treatment.

One of the most exciting psychiatric research findings in the last few decades begins to help dissolve a false dichotomy of medication versus psychotherapy. Whether using medication or "talk therapy", long-lasting changes can be effected in the neuronal circuitry through neuroplasticity.[22] For example, the "false alarm" seen in the basal ganglia with functional brain-scanning of OCD patients can be "switched off" in precisely the same way by either medication or cognitive-behavioural psychotherapy.[23] In other words, effective psychotherapy has particular brain effects!

BEGIN LOW, GO SLOW, REACH HIGH AND LONG

Research indicates that a second standard error made in treating psychiatric disorders in primary care settings is the failure to use medication at the correct dose or for the right duration. In depression, for example, it has been repeatedly suggested that tricyclic antidepressants are given at suboptimal doses.[24] In panic disorder, on the other hand, starting doses lower than those usually first given in depression are needed to avoid increased anxiety. Similarly, slow metabolisers, the elderly, or patients with brain damage may do well with lower doses of medication – although these factors should not preclude a dose increase for non- or partial responders when the currently prescribed dose is well-tolerated and without side effects.

Furthermore, patients need to be reminded that it might take several weeks before they notice any improvement in symptoms. In depression, for example, it may be helpful to continue a medication for six to eight weeks before deciding whether or not it is effective. If ineffective, dose-escalation strategies may be employed, or patients could be switched to an alternate drug for depression.[25,26]

In addition, medication often needs to be continued for a year or longer; in many psychiatric disorders, discontinuation of medication within a few months leads to relapse. Finally, when discontinuing medication, it is advisable to do this slowly and gradually (over several months) to prevent discontinuation reactions (which can occur with some antidepressants and antipsychotics) and to minimise the chances of symptom recurrence.[27] Cognitive behavioural therapy (CBT) or mindfulness-based cognitive therapy may also be useful adjuncts to prevent relapse of psychiatric symptoms when discontinuing pharmacotherapy.[28]

KEEP IT SIMPLE

Treatment regimens should be kept as simple as possible to improve patient acceptability and adherence. Once-a-day treatment regimens are preferable where possible. Similarly, monotherapy is generally preferable to polypharmacy, particularly in primary care settings.[29] Although there is a role for combining different psychiatric medications in treatment-resistant patients in speciality settings, this should ordinarily be avoided. In particular, it is rarely advisable to combine two medications from within the same class of agents (for example, two benzodiazepines or two tricyclic antidepressants).

ANTIDEPRESSANTS CAN BE GOOD ANXIOLYTICS

As detailed in Chapter 2, the term "antidepressant" is a relatively poor one. Although initially found helpful for the treatment of major depression, some of these agents are now recommended as first-line treatment for many of the anxiety disorders. In addition, they are the agents of choice for many patients who present with mixed anxiety and depression symptoms. For this reason, a more recent classification system for psychiatric medications is described in Chapter 2.

Compared with the benzodiazepines, the selective serotonin re-uptake inhibitors, for example, are not associated with the potential for dependence and are also useful for the treatment of panic disorder and social anxiety disorder (see Chapter 6). They may take longer to begin working, and concomitant short-term use of benzodiazepines may be helpful in patients with anxiety symptoms.[30,31]

MONITOR SIDE EFFECTS CAREFULLY

There is, to date, no psychiatric medication without side effects. Common or essential side effects should be outlined before medication is prescribed. For example, patients should be told that benzodiazepines may cause drowsiness and interfere with driving or other motor actions. Possible adverse effects are particularly important to consider during pregnancy and lactation.[32] We briefly address this issue where it seems most relevant (e.g., we mention the use of antidepressants during pregnancy in the chapter on depression); similar considerations naturally apply across disorders.

Side effects should be carefully monitored after medication is started. Sexual side effects, for example, may not be disclosed by patients unless the clinician specifically enquires about them.[33,34] Several medications require careful monitoring, using special investigations. Lithium, for example, is associated with hypothyroidism, so thyroid function requires ongoing assessment during its prescription. Similarly, electrocardiograms are necessary in patients on high doses of tricyclic antidepressants.

REMEMBER MEDICAL DISORDERS AND DRUG INTERACTIONS

Medical disorders may result in the need to adjust the prescription of particular psychiatric medications. For example, drugs with proconvulsant action need to be avoided in patients with a seizure disorder. Once again, examples are discussed most fully in the chapter on depression, but similar considerations also hold for other disorders.

A range of important drug interactions may occur with the prescription of psychiatric medications. These are discussed in more detail in Chapter 15. In particular, increased understanding of the cytochrome P450 enzyme system allows some prediction of what kinds of drug interactions may be particularly troublesome. Pharmacogenetic studies might further identify an individual's ability to absorb, distribute, metabolise or excrete various medications.[35,36] Finally, a careful history of herbal remedies and dietary supplements should always be taken, as many of these are psychotropic agents.[37]

CONSULT WHEN IT IS NECESSARY

Many of us pride ourselves on our ability to handle a wide range of patients without asking for help. Nevertheless, clinicians need to be aware of their limitations. In this world of rapid advances in medication, none of us can be apprised of all the latest developments. Decisions about whether to consult should err on the side of caution, particularly for patients with noticeably unusual or severe presentations. Patients with atypical psychiatric symptoms may benefit from a comprehensive specialist medical evaluation. Patients with suicidal or homicidal ideation may well require psychiatric hospitalisation before treatment in a general primary care setting is begun.

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. Washington, DC: American Psychiatric Publishing; 2013.
2. Ferenchick EK, Ramanuj P, Pincus HA. Depression in primary care: Part 1 – screening and diagnosis. BMJ. 2019 Apr 8;1794.
3. Goldberg D. The value of screening in patient populations with high prevalence of a disorder. BMC Med. 2014;12:14.
4. Thombs BD, Ziegelstein RC, Roseman M, *et al.* There Are No Randomised Controlled Trials That Support the United States Preventive Services Task Force Guideline on Screening for Depression in Primary Care: A Systematic Review. BMC Med. 2014;12:13.
5. Martin MS, Wells GA, Crocker AG, *et al.* Decision curve analysis as a framework to estimate the potential value of screening or other decision-making aids. Int J Methods Psychiatr Res. 2018 Mar;27(1).
6. Zhu M, Hong RH, Yang T, *et al.* The Efficacy of Measurement-Based Care for Depressive Disorders: Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Clin Psychiatry. 2021 Sep 28;82(5):21r14034.
7. Ramanuj P, Ferenchick EK, Pincus HA. Depression in primary care: Part 2 – management. BMJ. 2019 Apr 8;l835.
8. Henderson C, Evans-Lacko S, Thornicroft G. Mental illness stigma, help-seeking, and public health programs. Am J Public Health. 2013;103(5):777-80.
9. Horsfall J, Cleary M, Hunt GE. Stigma in mental health: Clients and professionals. Issues Ment Health Nurs. 2010;31(7):450-5.
10. Yakeley J, Hale R, Johnston J, *et al.* Psychiatry, subjectivity and emotion – deepening the medical model. Psychiatr Bull. 2014;38(3):97-101.
11. Slade M. Implementing shared decision making in routine mental health care. World Psychiatry. 2017 Jun;16(2):146-53.
12. Ahmed N, Barlow S, Reynolds L, *et al.* Mental Health Professionals' Perceived Barriers and Enablers to Shared Decision-Making in Risk Assessment and Risk Management: A Qualitative Systematic Review. BMC Psychiatry. 2021 Nov 25;21(1):594.
13. Zisman-Ilani Y, Chmielewska M, Dixon LB, *et al.* NICE shared decision making guidelines and mental health: Challenges for research, practice and implementation. BJPsych Open. 2021 Sep 2;7(5):e154.
14. Jakovljevic M. Non-adherence to medication: A challenge for person-centred pharmacotherapy to resolve the problem. Psychiatr Danub. 2014;2:358-63.
15. Wong-Anuchit C, Chantamit-O-Pas C, Schneider JK, *et al.* Motivational Interviewing-Based Compliance/Adherence Therapy Interventions to Improve Psychiatric Symptoms of People with Severe Mental Illness: Meta-Analysis. J Am Psychiatr Nurses Assoc. 2019 Apr;25(2):122-33.
16. Turner EH, Cipriani A, Furukawa TA, *et al.* Selective publication of antidepressant trials and its influence on apparent efficacy: Updated comparisons and meta-analyses of newer versus older trials. PLOS Med. 2022 Jan 19;19(1).
17. Huhn M, Tardy M, Spinelli LM, *et al.* Efficacy of pharmacotherapy and psychotherapy for adult psychiatric disorders: A systematic overview of meta-analyses. JAMA Psychiatry. 2014;71(6):706-15.
18. van Bronswijk S, Moopen N, Beijers L, *et al.* Effectiveness of Psychotherapy for Treatment-Resistant Depression: A Meta-Analysis and Meta-Regression. Psychol Med. 2019 Feb;49(3):366-79.
19. Miklowitz DJ, Efthimiou O, Furukawa TA, *et al.* Adjunctive Psychotherapy for Bipolar Disorder: A Systematic Review and Component Network Meta-Analysis. JAMA Psychiatry. 2021 Feb 1;78(2):141-50.
20. Bandelow B, Michaelis S, Wedekind D. Treatment of anxiety disorders. Dialogues Clin Neurosci. 2017 Jun;19(2):93-107.
21. Hunsley J, Elliott K, Therrien Z. The efficacy and effectiveness of psychological treatments for mood, anxiety, and related disorders. Can Psychol Can. 2014;55(3):161-76.
22. Kraus C, Castrén E, Kasper S, *et al.* Serotonin and neuroplasticity – links between molecular, functional and structural pathophysiology in depression. Neurosci Biobehav Rev. 2017 Jun;77:317-26.
23. Stein DJ. Advances in understanding the anxiety disorders: The cognitive-affective neuroscience of "false alarms." Ann Clin Psychiatry. 2006;18(3):173-82.
24. Isometsa E, Seppala I, Henriksson M, *et al.* Inadequate dosaging in general practice of tricyclic vs. other antidepressants for depression. Acta Psychiatr Scand. 1998;98(6):451-4.
25. Ruhé HG, Huyser J, Swinkels JA, *et al.* Dose Escalation for Insufficient Response to Standard-Dose Selective Serotonin Re-Uptake Inhibitors in Major Depressive Disorder: Systematic Review. Br J Psychiatry J Ment Sci. 2006 Oct;189:309-16.
26. Boyce P, Hopwood M, Morris G, *et al.* Switching antidepressants in the treatment of major depression: When, how and what to switch to? J Affect Disord. 2020 Jan 15;261:160-3.
27. Haddad PM, Anderson IM. Recognising and managing antidepressant discontinuation symptoms. Adv Psychiatr Treat. 2007;13(6):447-57.
28. Maund E, Stuart B, Moore M, *et al.* Managing Antidepressant Discontinuation: A Systematic Review. Ann Fam Med. 2019 Jan;17(1):52-60.

29. Haddad PM. Ten principles of good psychiatric prescribing. Medicine (Baltimore). 2012;40(12):674-5.
30. Starcevic V. The reappraisal of benzodiazepines in the treatment of anxiety and related disorders. Expert Rev Neurother. 2014;14(11):1275-86.
31. Bandelow B. Current and novel psychopharmacological drugs for anxiety disorders. Adv Exp Med Biol. 2020;1191:347-65.
32. Pereira PK, Lima LA, Legay LF, *et al.* Maternal mental disorders in pregnancy and the puerperium and risks to infant health. World J Clin Pediatr. 2012;1(4):20-3.
33. Zimmerman M, Galione JN, Attiullah N, *et al.* Underrecognition of clinically significant side effects in depressed outpatients. J Clin Psychiatry. 2010;71(4):484-90.
34. Kennedy SH. A review of antidepressant therapy in primary care: Current practices and future directions. Prim Care Companion CNS Disord. 2013;15(2).
35. Fabbri C, Porcelli S, Serretti A. From pharmacogenetics to pharmacogenomics: The way toward the personalisation of antidepressant treatment. Can J Psychiatry. 2014;59(2):62-75.
36. van Westrhenen R, van Schaik RHN, van Gelder T, *et al.* Policy and Practice Review: A First Guideline on the Use of Pharmacogenetics in Clinical Psychiatric Practice. Front Pharmacol. 2021;12.
37. Saxena A, Tripathi KP, Roy S, *et al.* Pharmacovigilance: Effects of herbal components on human drugs interactions involving cytochrome P450. Bio information. 2008;3(5):198-204.

2: Classifying Psychiatric Medications

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Psychiatric medications have traditionally been classified into antidepressants, anxiolytics, anti-psychotics, and mood stabilisers. Although this classification is in some ways very helpful, it is also problematic. The term "antidepressant", for example, is a particularly misleading one, insofar as these agents are also very useful in the anxiety disorders (Chapters 6-7), obsessive-compulsive and related disorders (Chapter 8) and post-traumatic stress disorder (Chapter 9).

A more scientific approach might be to classify medications in terms of their specific actions on neurotransmitters. The neuroscience-based nomenclature (NbN) classification, for example, covers 11 pharmacological domains and 10 modes of action.[1] However, this approach may entail a level of complexity that is not useful in primary care.

The compromise we make here is to divide psychiatric medications in the traditional way, with some additional NbN terminology where applicable, and then to sub-divide them in terms of their specific neurotransmitter actions. See Table 2.1. for commonly used NbN terminology, which focuses on neurotransmitter involvement.

This chapter includes tables listing the names of the major psychotropic medications currently available in South Africa, together with pertinent information about standard doses, dosage equivalents, and side effects. We are indebted to other authors for providing detailed information from which the tables are drawn.[2–6]

DRUGS FOR DEPRESSION

Antidepressant medications (see Table 2.2.) have been in use since the 1950s, when imipramine (the first tricyclic antidepressant [TCA]) and iproniazid (the first mono-amine oxidase inhibitor [MAOI]) were serendipitously found to elevate mood in depressed patients. The next important class of antidepressants was the selective serotonin re-uptake inhibitors (SSRIs); here, agents were intentionally developed with the aim of acting on a specific receptor. Since then, a number of medications have been developed with the aim of acting on multiple receptors.

Tricyclic and tetracyclic antidepressants

The TCAs (see Table 2.3.) have a range of actions, including serotonin (5HT) and noradrenaline

Table 2.1. Neuroscience-based nomenclature definitions

Former terminology (indication-based)	New terminology (pharmacologically-based)	Neurotransmitters and mode of action
Antidepressants	Drugs for depression	Multiple, depending on class – e.g., serotonin and noradrenaline re-uptake inhibition
Antipsychotics	Drugs for psychosis	Dopamine antagonists, serotonin antagonists, other effects
Anxiolytics	Drugs for anxiety	GABA agonists, sodium-channel blockers, glutamate modulators
Mood stabilisers	Drugs for relapse prevention	Glutamate modulators, GABA agonists, sodium-channel blockers
Hypnotics	Drugs for insomnia	GABA and melatonin agonists

Table 2.2. Drugs for depression (antidepressants)

Tricyclic antidepressants (TCAs)	Amitriptyline Clomipramine Dothiepin Imipramine Lofepramine Nortriptyline Trimipramine
Tetracyclic antidepressants (TCAs)	Maprotiline Mianserin
Mono-amine oxidase inhibitors (MAOIs)	Irreversible: tranylcypromine Reversible: moclobemide
Selective serotonin re-uptake inhibitors (SSRIs)	Citalopram Escitalopram Fluoxetine Fluvoxamine Paroxetine Sertraline
Selective noradrenaline re-uptake inhibitors (NRIs)	Reboxetine Atomoxetine
Serotonin-noradrenaline re-uptake inhibitors (SNRIs)	Duloxetine Desvenlafaxine Venlafaxine
Serotonin-2 antagonist and re-uptake inhibitors (SARIs)	Trazodone
Noradrenergic and specific serotonergic antidepressants (NaSSAs)	Mirtazapine
Noradrenaline-dopamine re-uptake inhibitors (NDRIs)	Bupropion
Melatonergic antidepressants	Agomelatine
Novel antidepressants	Vortioxetine

re-uptake inhibition, anticholinergic effects, and α1-noradrenergic blockade. The serotonin and noradrenaline re-uptake inhibition is responsible for the antidepressant effects. Anticholinergic effects are responsible for side effects such as dry mouth, blurred vision, urinary hesitancy, and constipation. Alpha-1 noradrenergic blockade is responsible for side effects, such as postural hypotension. These drugs are known to prolong the QTc interval due to the blocking of voltage-sensitive sodium channels, and are cardiotoxic in overdose.

The tricyclic antidepressants can be classified in various ways. In terms of site of action, they can be divided into those with more potent serotonergic effects (the most potent being clomipramine), those with more potent noradrenergic effects (such as lofepramine), and those which affect both neurotransmitters (e.g., imipramine). In terms of side effects, the tricyclics can be divided into secondary amines (which have more anticholinergic and α1-noradrenergic effects, e.g., amitriptyline) and tertiary amines (which have fewer of these side effects and are therefore particularly useful in the elderly, e.g., nortriptyline).

The tetracyclic maprotiline is a relatively noradrenergic re-uptake inhibitor, but also appears to be associated with a relatively high incidence of seizures. The tetracyclic mianserin, like the noradrenergic and specific serotonergic antidepressants (see Table 2.3.), is an α2-noradrenergic antagonist and a 5HT2 and 5HT3 antagonist, but it also has α1-noradrenergic antagonist properties which reduce its serotonergic effects, making it a predominantly noradrenergic agent. Mianserin has little to no central anticholinergic activity.

Table 2.3. Tricyclic and tetracyclic antidepressants

Chemical name	Trade name	Starting dose (mg/d)	Adult dose range (mg/d)	Sedation	Anticholinergic effects
Tricyclics					
Amitriptyline	Sandoz Amitryptiline HCL® Trepiline®	25 mg	150-300 mg	+++	+++
Clomipramine	Anafranil® Clomiden® Equinorm®	25-50 mg	100-250 mg	++	+++
Dothiepin	Sandoz Dothiepin HCL® Thaden®	25 mg	75-150 mg	+++	+++
Imipramine	Tofranil® Ethipramine®	25 mg	150-300 mg	++	+++
Lofepramine	Emdalen®	70 mg	140-210 mg	+	+
Trimipramine	Tydamine®	25-50 mg	150-300 mg	+++	+++
Tetracyclics					
Maprotiline	Ludiomil®	75 mg	100-225 mg	+++	++
Mianserin	Lantanon®	30 mg	30-90 mg	+++	+

+++ = high incidence/severity
++ = moderate
+ = low
- = very low

Mono-amine oxidase inhibitors

Mono-amine oxidase inhibitors (MAOIs) can be divided into those which are reversible and those which are irreversible. The older, irreversible agents have the reputation of being amongst the most powerful of the antidepressant agents and they remain a useful option for the treatment of refractory depression.[7] However, these agents also require strict avoidance of particular foods (such as cheese) and drugs (they can be fatal in combination with certain prescribed agents, such as pethidine and dextromethorphan). The reversible agents, of which only moclobemide is marketed, do not require any particular diet. Side effects of these agents include insomnia, agitation and gastro-intestinal disturbances. Do not prescribe MAOIs with other antidepressant agents.

Selective serotonin re-uptake inhibitors

The finding that TCAs work via serotonin and noradrenaline re-uptake inhibition led to a search for compounds that had these effects, but did not affect the cholinergic system. Fluoxetine was the first of the selective serotonin re-uptake inhibitors (SSRIs) (see Table 2.4.). Side effects of these agents are primarily caused by serotonin re-uptake inhibition and include transient nausea and, more importantly, weight gain and sexual side effects (including erectile dysfunction and delayed ejaculation in men, and anorgasmia in women).

While each of the tricyclic and tetracyclic antidepressants (TCAs) is selective for serotonin re-uptake inhibition, they have subtle differences, including differences in their half-life (fluoxetine, for example, has a particularly long half-life, so is useful in patients who occasionally forget to take medication). There are slight effects on non-serotonin receptors (paroxetine, for example, may have some anticholinergic effects, which may have a useful sedative effect in some patients), and on the P450 system (citalopram, escitalopram, and sertraline, for example, have particularly few P450 effects and therefore fewer drug interactions).[8]

Table 2.4. Selective serotonin re-uptake inhibitors

Chemical name	Trade name	Starting dose (mg/d)	Adult dose range (mg/d)(*)	Weight gain	Sexual dysfunction
Citalopram	Cipramil® Numerous generics	20 mg	20-40 mg	+	++
Escitalopram	Cipralex® Numerous generics	10 mg	10-20 mg	+	++
Fluoxetine	Prozac® Lorien® Numerous generics	20 mg	20-60 mg	+	++
Fluvoxamine	Luvox® Faverin® Fluvoxamine-Hexal®	50 mg	50-200 mg	+	++
Paroxetine	Aropax® Numerous generics	20 mg	20-50 mg	++	+++
Paroxetine CR	Aropax® CR	25 mg	25-50 mg	++	+++
Sertraline	Zoloft® Numerous generics	50 mg	50-200 mg	+	++

(*) Highest doses used particularly in obsessive-compulsive disorder
+++ = high incidence/severity
++ = moderate
+ = low
– = very low

Selective noradrenaline re-uptake inhibitors

Selective noradrenaline re-uptake inhibitors (NRI) include reboxetine (Edronax®) and atomoxetine (Strattera®). Side effects of these agents are naturally due to noradrenaline re-uptake inhibition, and include sweating, insomnia, and vertigo.

Serotonin-noradrenaline re-uptake inhibitors

This class (SNRIs) includes the drugs venlafaxine, duloxetine and desvenlafaxine (see Table 2.5.). Like the TCAs, they are serotonin and noradrenaline re-uptake inhibitors. However, unlike the tricyclic antidepressants, they have few anticholinergic effects.

Venlafaxine acts as an SSRI at lower doses, and an SNRI at higher doses.[9] Amongst the important side effects to be aware of is the possibility of increased blood pressure, particularly at high doses. An extended-release form of venlafaxine is also available, allowing for once-daily dosing. Desvenlafaxine is a synthetic form of the major active metabolite of venlafaxine.

In contrast to venlafaxine, duloxetine is a balanced inhibitor of both serotonin and noradrenaline re-uptake, but may be less well tolerated than other SNRIs.[10] Hepatotoxicity has been reported with duloxetine.[11]

Serotonin antagonists and re-uptake inhibitors (SARIs)

Trazodone is a serotonin re-uptake inhibitor, but also has 5HT2 receptor antagonist properties. 5HT2 antagonist effects turn out to be useful for counteracting the sexual side effects of the serotonin re-uptake inhibitors. Indeed, trazodone has been associated with priapism.[12] Drowsiness and sedation is a commonly reported side effect, together with headache, dizziness and restlessness.

Noradrenergic and specific serotonergic antidepressants (NaSSAs)

Mirtazapine is a compound which acts as an α2-noradrenergic antagonist and as a 5HT2 and 5HT3 antagonist.[2] As α2-noradrenergic receptors are responsible for negative feedback,

Table 2.5. Serotonin noradrenaline re-uptake inhibitors

Chemical name	Trade name	Starting dose (mg/d)	Adult dose range (mg/d)(*)	Weight gain	Sexual dysfunction
Duloxetine	Cymbalta® Cymgen® Yelate®	30-60 mg	30-120 mg	–	++
Desvenlafaxine	Pristiq®	50 mg	50 mg	–	++
Venlafaxine	Efexor XR® Efegen XR® Illovex SR® Venlor® Odiven®	37.5-75 mg	75-375 mg	–	++

+++ = high incidence/severity
++ = moderate
+ = low
– = very low

antagonism results in increased noradrenergic neurotransmission. These receptors also act as heteroreceptors on serotonin neurons, thereby increasing serotonergic neurotransmission. The presence of 5HT2 antagonism is associated with a lack of sexual side effects. Mirtazapine also has histaminergic effects via H1 antagonism, resulting in sedation and weight gain.

Noradrenaline-dopamine re-uptake inhibitors (NDRIs)

Bupropion has weak re-uptake-blocking properties on dopamine and noradrenaline, and is metabolised to a number of active metabolites, some of which are more potent re-uptake blockers than the parent molecule. Bupropion is available as a slow-release (SR) or extended-release (XR) formulation. At high doses, bupropion may be epileptogenic in patients predisposed to seizures.[13] In addition to its antidepressant properties, bupropion is efficacious in treating nicotine dependence.[14]

Melatonergic antidepressants

Agomelatine is an agonist at melatonin-1 (MT1) and melatonin-2 (MT2) receptors, and an antagonist at 5HT2 receptors. These simultaneous actions are thought to enhance neurogenesis, resynchronise circadian rhythms (which are often disrupted in depression), and increase levels of dopamine and noradrenaline in the prefrontal cortex. It is an effective treatment for major depressive disorder and generalised anxiety disorder.[15-17]

NMDA receptor antagonists (glutamate antagonists)

Ketamine is a glutamate antagonist acting diffusely at the NMDA receptors throughout the brain. It can be administered intravenously or intranasally, and has shown some promising results in randomised clinical trials of treatment-resistant depression.[18,19] The role of ketamine in the treatment of refractory depression is discussed in Chapter 3.[20]

DRUGS FOR PSYCHOSIS

Antipsychotic agents may be divided into those that are more typical and those that are more atypical (see Table 2.6.). This distinction remains incompletely understood and the term "antipsychotic" is again not an entirely accurate one, with the NbN describing these agents as drugs for psychosis, and noting that they are predominantly dopamine antagonists, with some agents having additional activity at other neurotransmitter receptors. These agents are helpful in the treatment of psychotic disorders such as schizophrenia, mood disorders such as depression with psychosis (Chapter 5), manic episodes of bipolar disorder (Chapter 12), and for behavioural and psychological symptoms associated with dementia (Chapter 13).

D2 receptor antagonists (typical antipsychotics)

Chlorpromazine was the first drug discovered to have antipsychotic effects in patients with schizophrenia. As a class, the typical antipsychotics (also called first-generation

Continued on page 14

Table 2.6. Drugs for psychosis (antipsychotics)

Chemical name	Trade name	Starting dose	Usual therapeutic dose range (mg/d)(*)	Anti-cholinergic effects	Extrapyra-midal side effects	Cardio-metabolic side effects
Typical						
Chlorpromazine	Largactil® Numerous generics	25 mg TDS	75-300 mg	+++	+	+++
Flupenthixol	Fluanxol®	1 mg/d (oral) 10 mg IMI	2-3 mg/d 20-60 mg 2-4 weekly IMI	++	+++	+
Fluphenazine	Modecate®	12,5 mg IMI	12,5-25 mg 2-4 weekly IMI	+	+++	+
Haloperidol	Serenace® Sandoz Halopridol®	0,5 mg BD	2-10 mg/d	+	+++	+
Pimozide	Orap®	1-4 mg/d	4-8 mg/d	+	+	+
Sulpiride	Elgonyl® Espiride Sandoz Sulpiride	100-150 mg/d	300-800 mg/d	–	– or +	+
Trifluoperazine	Stelazine®	2-5 mg BD	15-20 mg/d	–	+++	+
Zuclopenthixol	Clopixol®	50-100 mg IMI	200-400 mg 2-4 weekly IMI	++	++	++
Atypical						
Amisulpiride	Solian®	200-400 mg/d	400-1 200 mg	–	+	++
Aripiprazole	Abilify®	10-15 mg/d	10-15 mg	–	+	–
Brexipiprazole	Rexulti®	1 mg/d	2-4 mg	–	+	–
Clozapine	Clozapine	12,5-25 mg/d	300-600 mg/d	+++	- or +	+++
Olanzapine	Zyprexa® Numerous generics	5-10 mg/d	10-20 mg/d	+	+	+++
Paliperidone	Invega®	6 mg/d	6-12 mg/d	+	+	++
Quetiapine	Seroquel® Numerous generics	50 mg/d	300-450 mg/d	+	–	++
Risperidone	Risperdal® Numerous generics	2 mg/d	4-8 mg/d	+	++	++
Risperidone Depot	Risperdal® Consta	25 mg IMI	25 mg 2-weekly IMI	As for risperidone		
Ziprasidone	Geodon®	40-80 mg/d	80-160 mg/d	–	+	–

(*) Doses higher than this may be required in certain cases; and should be made in line with approved drug formularies
+++ = high incidence/severity
++ = moderate
+ = low
– = very low

antipsychotics) share the common pharmacological property of dopamine (D2) receptor antagonism. Blockade of D2 circuits is responsible for many of the therapeutic effects and side effects of these agents.[2] Blockade of mesolimbic circuits results in antipsychotic effects. Blockade of nigrostriatal pathways causes extrapyramidal motor side effects, including acute dystonia, parkinsonism, akathisia, and tardive dyskinesia. Blockade of tubero-infundibular pathways is responsible for hyperprolactinaemia, and blockade of cells in the area postraema results in anti-emetic effects.

These agents do, however, have other neurotransmitter receptor affinities (with corresponding side effects), including muscarinic acetylcholine blockade (causing anticholinergic adverse events), α1-noradrenergic receptor blockade (causing postural hypotension) and histamine (H1) blockade (causing sedation and weight gain). Each of these medications may have additional adverse effects that are particular to that agent; haloperidol, for example, may cause pigmentary retinopathy and QTc prolongation.

Typical antipsychotics can be divided into high-potency agents and low-potency agents. High-potency agents are more likely to lead to extrapyramidal neurological side effects, but have fewer anticholinergic side effects. Low-potency agents are less likely to have extrapyramidal effects, but are more likely to be associated with anticholinergic effects (which can be useful when sedation is needed) and postural hypotension.

D2 receptor antagonists with 5HT2A antagonist activity and partial D2 antagonists (atypical antipsychotics)

The atypical antipsychotics (also called second-generation antipsychotics) share the dopamine antagonist properties of typical antipsychotics, but have the additional property of serotonin antagonism at the 5HT2A receptors, predominantly in the striatum. This coupling of serotonin and dopamine antagonism leads to a clinical profile of fewer extrapyramidal symptoms and less hyperprolactinaemia compared to typical antipsychotics, making this class of drugs "atypical". Furthermore, agents in this class interact with multiple other dopamine- and serotonin-receptor subtypes, as well as other neurotransmitter systems. Each drug in this class has an individual binding profile, responsible for both its therapeutic- and side effects.

Atypical antipsychotics share a class warning for cardiometabolic risk; including weight gain, dyslipidaemia, impaired glucose tolerance and diabetes mellitus.[21] The precise mechanism of these changes is unknown, although there appears to be a spectrum of metabolic risk among the various agents, with clozapine and olanzapine having the greatest propensity.

Clozapine is the oldest of the atypical anti-psychotics. This agent requires careful monitoring because of idiosyncratic agranulocytosis, myocarditis and paralytic ileus.[22,23] However, clozapine has been shown to be helpful in patients who have failed to respond to multiple trials of different antipsychotics and is the medication of choice for treatment-resistant schizophrenia.[24-26] The other atypical antipsychotics have a safer side-effect profile than clozapine. Clozapine has shown better efficacy than most antipsychotic agents in schizophrenia and bipolar disorder with and without treatment resistance.[24,27]

Amisulpiride has been called an "atypical typical" agent. This substituted benzamide is a highly selective D2/D3 receptor antagonist, but at low doses it preferentially blocks presynaptic dopamine autoreceptors, possibly facilitating dopaminergic transmission in frontal areas and reducing negative symptoms.[28] It is a partial D2 agonist, meaning that it still allows for some neurotransmission via these receptors, which results in less complete D2 antagonism and hence reduction of the potential for side effects.[2]

Other novel antipsychotics such as brexipiprazole (partial D2 antagonist), aripiprazole (partial D2 antagonist), cariprazine (partial D2 antagonist and 5HT2 antagonist), lurasidone (D2 and 5HT2 antagonist) and lumateperone (D2 and 5HT2 antagonist) have shown some promising results, although only brexpiprazole and aripiprazole are currently available in South Africa.[29,30]

DRUGS FOR ANXIETY (ANXIOLYTICS)

Several classes of agents are used predominantly for anxiolytic or sedative actions. The barbiturates are useful for anxiolysis and sedation, but they are no longer widely prescribed because of their high risk for dependence and their low therapeutic index. The benzodiazepines continue to be widely prescribed, although antidepressants are now considered first-line agents for most anxiety disorders.[31] Newer agents, the non-benzodiazepine GABA agonists, may

be particularly useful in the treatment of insomnia.[32] The azapirones, such as buspirone, may have a role in the treatment of generalised anxiety disorder.[31] More recently, the α2δ ligands gabapentin and pregabalin have been shown to have anxiolytic properties.[31]

GABA-A allosteric modulators (benzodiazepines)

The benzodiazepines (see Table 2.7.) are α-aminobutyric acid (GABA) agonists which act as positive allosteric modulators at the GABAA receptor.[1] GABA agonism is associated with a decrease in anxiety, an increase in sedation, cognitive slowing, anticonvulsant activity, and muscle relaxation. These agents can be associated with abuse and dependence, and should only be prescribed for short periods of time.[33]

The benzodiazepines can be divided into those with immediate onset and those with longer onset, those which get distributed primarily into fat and those which don't, and those with short elimination half-lives and those with long elimination half-lives.

- Rapid onset of action may be relatively useful for the treatment of insomnia.
- Lack of fat distribution may be useful in acute treatment of seizures (a single dose of lorazepam has a longer action than a

Table 2.7. Benzodiazepines

Chemical name	Trade name	Usual single dose (mg)	Approximate equivalent dose (mg)
Ultra-short-acting (half-life: <6 hours)			
Midazolam	Dormicum	7,5 mg	15 mg
Triazolam	Halcion	0,125 mg-0,25 mg	0,5 mg
Short-acting (half-life: 6-12 hours)			
Brotizolam	Lendormin	0,25 mg	5 mg
Loprazolam	Dormonoct	1-2 mg	2 mg
Lormetazepam	Loramet	1 mg	1 mg
Oxazepam	Serapax	10-15 mg	30 mg
Temazepam	Normison	10-30 mg	30 mg
Intermediate-acting (half-life: 12-24 hours)			
Alprazolam	Xanor	0,25-0,5 mg	0,5 mg
Bromazepam	Lexotan	2-6 mg	3 mg
Lorazepam	Ativan	0,5-2 mg	2 mg
Long-acting (half-life: >24 hours)			
Chlordiazepoxide	Librium	12-25 mg	25 mg
Clobazam	Urbanol	10-20 mg	20 mg
Clonazepam	Rivotril	0,25-0,5 mg	2 mg
Diazepam	Valium	2-10 mg	10 mg
Flunitrazepam	Rohypnol	0,5-2 mg	1 mg
Nitrazepam	Arem	5-10 mg	10 mg
Prazepam	Demetrin	10-20 mg	15 mg
Non-benzodiazepine drugs for insomnia (hypnotics)			
Zolpidem	Stilnox	10 mg	20 mg
Zopiclone	Imovane	7,5 mg	15 mg

single dose of diazepam and is therefore a good choice in this situation).
- Long elimination half-life is associated with marked hangover effects and with increased risk of sedation (diazepam, for example, has a longer elimination half-life than lorazepam and is associated with increased incidence of hip fractures from falls in the elderly). On the other hand, drugs with short elimination half-lives require more frequent dosing, have more pronounced peaks and troughs, more rapid and severe withdrawal, and more anterograde amnesia (e.g., triazolam has been associated with this effect).

Other GABA agonists (non-benzodiazepine GABA agonists)

Zolpidem and zopiclone are non-benzodiazepines that nevertheless act as partial agonists at the benzodiazepine receptor of the GABA complex. These agents were designed to induce mild sedation, but also to have less cognitive impairment and dependence potential than the benzodiazepines.[34] Despite this, potential for dependence is present and cautious prescribing is once again recommended.[35] Additionally, these drugs are associated with cognitive impairment and falls in the elderly.[36]

5HT1A partial agonists (azapirones)

Buspirone is a 5HT1A partial agonist. 5HT1A receptors are presynaptic somatodendritic autoreceptors, and their partial agonism may be useful in optimising serotonergic function. Buspirone has been shown to be effective in decreasing anxiety after being administered for several weeks. It may therefore be a useful agent in patients with generalised anxiety disorder.[31] It has relatively few side effects.

Glutamate modulators (α2δ ligands)

Pregabalin and gabapentin bind to the α2δ subunit of presynaptic voltage-sensitive calcium channels, blocking the release of excitatory neurotransmitter glutamate, hypothetically reducing fear and worry. Pregabalin is efficacious in the acute and maintenance treatment of generalised anxiety disorder and social anxiety disorder, and pregabalin and gabapentin may be effective in the acute treatment of panic disorder.[31]

DRUGS FOR RELAPSE PREVENTION (MOOD STABILISERS)

Lithium was the first agent found to be useful in stabilising mood in bipolar disorder (previously called manic-depression). A number of anticonvulsant agents have also been found useful in this disorder, with valproate the most widely used (Chapter 12). These agents work by decreasing glutamatergic neurotransmission either directly or by stimulating GABA activity or through interactions with sodium channels.[1,2] Additionally, both typical and atypical antipsychotics have rapid mood-stabilising properties, and may be a treatment of choice for acute manic or depressive bipolar episodes.[37]

Lithium

The effects of lithium are not entirely understood. Nevertheless, since serendipitously found to stabilise mood in bipolar disorder it has become one of the most important agents in the psychiatric armamentarium. Importantly, lithium has a narrow therapeutic index, and careful monitoring of blood levels is therefore required.[38] Side effects of lithium include hypothyroidism, diuresis, and increased white blood cell count. In high doses, the CNS effects of lithium (tremor, memory loss, drowsiness, seizure) are dangerous and should be managed as an emergency.[39]

Voltage-gated calcium- and sodium-channel blockers (anticonvulsants)

Anticonvulsants (see Table 2.8.) are used in the treatment of bipolar disorder. Bipolar disorder is now understood to involve a 'kindling' effect; each subsequent episode may be more easily triggered and more difficult to treat.[40] It is therefore crucial to continue medication lifelong; after discontinuing a medication, the patient may respond less favourably to that agent in future. Anticonvulsants, alone, or together with lithium or antipsychotics, play a useful therapeutic role.[37] Although valproate is the most widely used, there are also efficacy data for carbamazepine, gabapentin, and lamotrigine.[41-43] A controlled-release (CR) form of valproate is now available.

Table 2.8. Anticonvulsants

Chemical name	Trade name	Starting dose (mg/d)	Adult dose range (mg/d)	Rare but serious side effects
Carbamazepine	Tegretol	100-200 mg	400-600 mg	• Agranulocytosis • Aplastic anaemia • Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) • Hepatic failure
Gabapentin	Neurontin	300-400 mg	900-1 800 mg	• Leucopenia Thrombocytopenia
Lamotrigine	Lamictin	25 mg	100-400 mg	• SJS/TEN
Pregabalin	Lyrica	150 mg	150-300 mg	• Neutropenia Rhabdomyolysis
Sodium valproate*	Epilim CR (controlled-release)	600-900 mg	1 000-2 000 mg	• Agranulocytosis • Aplasic anaemia • SJS/TEN
Valproic acid	Convulox	600-900 mg	1 000-2 000 mg	• Hepatic failure • Pancreatitis

(*) Converted to valproic acid (the active drug); 200 mg of sodium valproate is equivalent therapeutically to 150 mg of valproic acid

MISCELLANEOUS AGENTS

A range of other agents can be used for psychiatric purposes.

Dopamine and norepinephrine re-uptake inhibitors and releasers (stimulants)

Methylphenidate is a psychostimulant that displaces dopamine and noradrenaline from presynaptic nerve terminals and inhibits their re-uptake. This agent is used in the treatment of attention deficit hyperactivity disorder (ADHD), and in various other conditions, such as narcolepsy.[44-46] The media have raised concerns about its safety, abuse potential, and over-prescription in ADHD.[47] Nevertheless, properly used, this agent is safe and effective.

Agents that facilitate dopaminergic transmission may also have other indications in psychiatry. For example, the dopamine-releasing agent amantadine is used in treating neuroleptic-induced parkinsonism.[48] Also, levodopa and dopamine agonists (bromocriptine, pramipexole, ropinirole) are used in the treatment of idiopathic Parkinson's disease and restless legs syndrome.[49] Indirect and direct dopamine agonists may also be useful in the treatment of apathy following stroke or in dementia.[50,51]

Adrenergic and noradrenergic antagonists

Beta-blockers are used in the treatment of performance anxiety (Chapter 6). They are, however, ineffective in the treatment of other forms of anxiety. Systematic reviews have not demonstrated any association between beta blockers and depression.[52,53] Clonidine and guanfacine are α2-agonists (reducing adrenergic transmission), and are used in the treatment of Tourette's disorder, in ADHD and in opioid withdrawal.[54-56]

Serotonergic agents

Several 5HT1D agonists are marketed for the treatment of migraine[57]; their role in the treatment of neuropsychiatric disorders has not yet been defined. Ondansetron is a selective 5HT3 antagonist used in the treatment of nausea and vomiting, and may have some benefit in treating negative symptoms of schizophrenia.[58,59]

Cholinergic agents

The cholinesterase inhibitors donepezil, rivastigmine and galantamine are used in the

treatment of the cognitive and behavioural symptoms of Alzheimer's disease (Chapter 13). These agents have somewhat different profiles; donepezil is selective for acetylcholinesterase, rivastigmine inhibits both acetylcholinesterase and butyrylcholinesterase, and galantamine also modulates cholinergic nicotinic receptors.[2] These agents have a role in the treatment of other neurocognitive disorders, with evidence of their value in Parkinson's disease, Parkinson's disease with dementia, and dementia with Lewy bodies.[60]

Anticholinergic agents (biperiden, trihexyphenidyl, orphenadrine) are used in the treatment of neuroleptic-induced dystonia and parkinsonism.[38]

Histaminic agents

Antihistamines are used in the treatment of neuroleptic-induced parkinsonism. Hydroxyzine, which also has 5HT2-blocking properties, has been found effective in the treatment of generalised anxiety disorder (Chapter 7).[61]

Glutamatergic agents

Whereas GABA is the most common inhibitory neurotransmitter, glutamate is the predominant excitatory neurotransmitter in the brain. Glutamate acts at a number of receptors, including the N-methyl-D-aspartate (NMDA) receptor. Several medications mentioned previously, including ketamine and some of the anticonvulsants, appear to exert their effects via the glutamatergic system.

Memantine is an NMDA receptor antagonist used in the treatment of moderate-severe Alzheimer's disease, to temporarily alleviate symptoms such as apathy, and slow progression of the illness.[51,62,63]

Acamprosate or calcium acetyl-homotaurine, which is useful in the treatment of alcohol dependence, may act by blocking glutamate at NMDA and metabotropic glutamate receptors, mitigating glutamatergic hypersensitivity.[64]

N-acetyl-cysteine (NAC) is a glutamate modulator that has been trialled in a number of psychiatric conditions. It has shown promising efficacy in schizophrenia, bipolar disorder, substance use disorders, trichotillomania, and excoriation disorder.[65-72]

Opioid agents

Naltrexone is an opioid antagonist. It may be helpful in the relapse-prevention treatment of alcohol and opioid dependence.[64]

Several opioid agonists are available for the acute and maintenance treatment of opioid-use disorders. Methadone is a long-acting, full opioid agonist that carries a high dependence potential and a low lethal dose. Buprenorphine (Subutex®) is a partial opioid agonist, available as a sublingual tablet, with a high affinity for the μ-opioid receptors. The partial agonist properties of this drug mean it has a lower comparable risk of toxicity and overdose compared to methadone. Buprenorphine is also available as a fixed-dose combination (Suboxone®) with the opioid antagonist naloxone to prevent intravenous and nasal abuse of buprenorphine.

Hormones/peptides

Thyroid hormone is used in the treatment of refractory depression and refractory bipolar disorder (Chapters 5, 11).[73-75] Oestrogens may have a role in the treatment of women with postpartum depression, or depression in the perimenopausal period (Chapter 5).[76,77] Brexanolone has shown efficacy for postpartum depression, however is not yet available in South Africa.[78] Melatonin has been used in the treatment of the jet lag subtype of circadian rhythm disorder (Chapter 10).[79] Desmopressin, a modified analogue of vasopressin, has been used in the treatment of enuresis.[80]

Cannabinoids

Cannabinoids such as tetrahydrocannabinol (THC) and cannabidiol (CBD) are two of the multiple cannabinoids found in the *Cannabis sativa* and *Cannabis indica* plants. THC produces the high associated with marijuana use, but CBD is FDA-approved for the treatment of seizures associated with Lennox Gastaut syndrome (LGS), Dravet syndrome (DS), or tuberous sclerosis complex (TSC).[81] The role of cannabinoids in treating psychiatric conditions is less well-established[82], but with their increasing availability, many patients may try these preparations as over-the-counter options.[83]

Other medications

Disulfiram blocks the metabolism of acetaldehyde, a breakdown product of alcohol. Accumulation of acetaldehyde leads to flushing, nausea, vomiting and distressing autonomic symptoms. Disulfiram (250 mg daily, or 125 mg daily in older patients) has therefore been used in the treatment of alcohol dependence.[84]

Flumazenil is a benzodiazepine receptor antagonist, used in the treatment of benzodiazepine overdose.

Dantrolene sodium, a hydantoin derivative, is a long-acting muscle relaxant. In work done at the University of Cape Town, it was initially developed for use in malignant hyperthermia, and it has been suggested for managing neuroleptic malignant syndrome.[85]

Complementary therapies

Many herbal remedies have been claimed to be effective for the treatment of psychiatric disorders.[86,87] Given that such products often have extremely high variability in their chemical components, and given the high placebo response rates in drug trials in psychiatry, such claims should be reviewed cautiously.[88] Furthermore, it is important to remember that effective psychotropic agents, whether synthetic or herbal, have the potential for adverse events and drug interactions. These should therefore be specifically addressed when taking a drug history.

One of the best studied herbal remedies in psychiatry is St. John's Wort.[89] Now available in standardised form, this agent may have serotonin re-uptake properties and appears to be effective in the treatment of mild to moderate depression. It may have drug interactions with synthetic agents, and like effective antidepressants, can precipitate mania. Other herbal agents on which research has been undertaken include *Ginkgo biloba* in dementia[90], kava for anxiety[91], ginseng (an "adaptogen") for cognitive and mood enhancement[92], and yohimbine for erectile dysfunction.[93] Increasingly, such agents are being included in pharmacotherapy algorithms and guidelines where appropriate.

Claims about the value of nutritional supplements for the treatment of psychiatric disorders also deserve scepticism in the absence of rigorous studies, although there is growing evidence of the value of a range of dietary supplements, including probiotics, in managing symptoms of many mental disorders.[94-98]

The role of serotonergic psychedelics in the treatment of depression and posttraumatic stress disorder is an area that warrants further research.[99,100]

ADDITIONAL READING

1. Rossiter D, University of Cape Town. Division of Clinical Pharmacology. South African medicines formulary (13th edition). Erasmuskloof, Pretoria: Health and Medical Publishing Group; 2020.
2. Stahl SM. Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications (5th edition). Cambridge University Press; 2021.
3. Stahl SM. The Prescriber's Guide: Stahl's essential psychopharmacology (6th edition). Cambridge University Press; 2017.
4. Taylor DM, Barnes TR, Young AH. The Maudsley prescribing guidelines in psychiatry. 14th edition. Chichester, West Sussex. Hoboken, NJ. John Wiley & Sons; 2021.

REFERENCES

1. Zohar J, Stahl S, Moller H-J, *et al.* A review of the current nomenclature for psychotropic agents and an introduction to the Neuroscience-based Nomenclature. Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol. 2015 Dec; 25(12):2318-25.
2. Stahl SM. Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications (5th edition): Cambridge University Press; 2021.
3. Talmud J. Daily Drug Use: A 1994 Update. A Guide for the Health Professional: Tincture Press; 1994.
4. Turner L. Daily Drug Use: A Guide for the Health Professional. Cape Western Branch of the Pharmaceutical Society of South Africa; 2010.
5. Rossiter D. South African Medicines Formulary. Rondebosch, South Africa: Health and Medical Publishing Group; 2014.
6. Taylor P. Clinical decision making: From theory to practice. JAMA. 1996;276(17):1445.
7. Thase ME. The role of mono-amine oxidase inhibitors in depression treatment guidelines. J Clin Psychiatry. 2012;1:10-6.
8. Stahl SM. Stahl's Essential Psychopharmacology: the Prescriber's Guide – Antidepressants. 6th ed. Cambridge; New York: Cambridge University Press; 2017.
9. Stahl SM, Grady MM, Moret C, *et al.* SNRIs: their pharmacology, clinical efficacy, and tolerability in comparison with other classes of antidepressants. CNS Spectr. 2005;10(9):732-47.
10. Cipriani A, Koesters M, Furukawa TA, *et al.* Duloxetine versus other anti-depressive agents for depression. Cochrane Database Syst Rev. 2012(10):CD006533.
11. Voican CS, Corruble E, Naveau S, *et al.* Anti-depressant-induced liver injury: A review for clinicians. Am J Psychiatry. 2014 Apr;171(4):404-15.
12. Fagiolini A, Comandini A, Catena Dell'Osso M, *et al.* Rediscovering trazodone for the treatment of major depressive disorder. CNS Drugs. 2012;26(12):1033-49.
13. Montgomery SA. Antidepressants and seizures: Emphasis on newer agents and clinical implications. Int J Clin Pr. 2005;59(12):1435-40.

14. Howes S, Hartmann-Boyce J, Livingstone-Banks J, *et al.* Antidepressants for smoking cessation. Cochrane Database Syst Rev. 2020;(4).
15. De Berardis D, Fornaro M, Serroni N, *et al.* Agomelatine beyond borders: Current evidences of its efficacy in disorders other than major depression. Int J Mol Sci. 2015;16(1):1111-30.
16. Taylor D, Sparshatt A, Varma S, *et al.* Antidepressant Efficacy of Agomelatine: Meta-Analysis of Published and Unpublished Studies. BMJ. 2014;348:1888.
17. Wang S-M, Woo YS, Kim N-Y, *et al.* Agomelatine for the Treatment of Generalized Anxiety Disorder: A Meta-Analysis. Clin Psychopharmacol Neurosci. 2020 Aug 31;18(3):423-33.
18. Rosenblat JD, Carvalho AF, Li M, *et al.* Oral Ketamine for Depression: A Systematic Review. J Clin Psychiatry. 2019 Apr 16;80(3):13514.
19. Bahji A, Vazquez GH, Zarate CA. Comparative Efficacy of Racemic Ketamine and Esketamine for Depression: A Systematic Review and Meta-Analysis. J Affect Disord. 2021 Jan 1;278:542-55.
20. Serafini G, Howland RH, Rovedi F, *et al.* The Role of Ketamine in Treatment-Resistant Depression: A Systematic Review. Curr Neuropharmacol. 2014 Sep;12(5):444-61.
21. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: A comprehensive literature review. CNS Drugs. 2005;1:1-93.
22. Lundblad W, Azzam PN, Gopalan P, *et al.* Medical management of patients on clozapine: A guide for internists. J Hosp Med. 2015;
23. de Leon J, Ruan C-J, Schoretsanitis G, *et al.* A rational use of clozapine based on adverse drug reactions, pharmacokinetics, and clinical pharmacopsychology. Psychother Psychosom. 2020;89(4):200-14.
24. Mizuno Y, McCutcheon RA, Brugger SP, *et al.* Heterogeneity and Efficacy of Antipsychotic Treatment for Schizophrenia with or without Treatment Resistance: A Meta-Analysis. Neuropsychopharmacology. 2020 Mar;45(4):622-31.
25. Wahlbeck K, Cheine M, Essali A, *et al.* Evidence of Clozapine's Effectiveness in Schizophrenia: A Systematic Review and Meta-Analysis of Randomized Trials. Am J Psychiatry. 1999 Jul;156(7):990-9.
26. Krause M, Zhu Y, Huhn M, *et al.* Antipsychotic Drugs for Patients with Schizophrenia and Predominant or Prominent Negative Symptoms: A Systematic Review and Meta-Analysis. Eur Arch Psychiatry Clin Neurosci. 2018 Oct;268(7):625-39.
27. Li X-B, Tang Y-L, Wang C-Y, *et al.* Clozapine for Treatment-Resistant Bipolar Disorder: A Systematic Review. Bipolar Disord. 2015 May;17(3):235-47.
28. Leucht S. Amisulpride: A selective dopamine antagonist and atypical antipsychotic: Results of a Meta-Analysis of randomized controlled trials. Int J Neuropsychopharmacol. 2004;1:15-20.
29. Corponi F, Fabbri C, Bitter I, *et al.* Novel antipsychotics specificity profile: A clinically oriented review of lurasidone, brexpiprazole, cariprazine and lumateperone. Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol. 2019 Sep;29(9):971-85.
30. Kishi T, Ikuta T, Matsuda Y, *et al.* Aripiprazole vs. Brexpiprazole for Acute Schizophrenia: A Systematic Review and Network Meta-Analysis. Psychopharmacology. 2020 May;237(5):1459-70.
31. Baldwin DS, Anderson IM, Nutt DJ, *et al.* Evidence-based pharmacological treatment of anxiety disorders, posttraumatic stress disorder and obsessive-compulsive disorder: A revision of the 2005 guidelines from the British Association for Psychopharmacology. J Psychopharmacol. 2014;28(5):403-39.
32. Porwal A, Yadav YC, Pathak K, *et al.* An update on assessment, therapeutic management, and patents on insomnia. BioMed Res Int. 2021;2021:1-19.
33. Longo LP, Addiction JB, Part I. Benzodiazepines – side effects, abuse risk and alternatives. Am Fam Physician. 2000;61(7):2121-8.
34. Buscemi N, Vandermeer B, Friesen C, *et al.* The Efficacy and Safety of Drug Treatments for Chronic Insomnia in Adults: A Meta-Analysis of RCTs. J Gen Intern Med. 2007;22(9):1335-50.
35. Rios P, Cardoso R, Morra D, *et al.* Comparative effectiveness and safety of pharmacological and non-pharmacological interventions for insomnia: An overview of reviews. Syst Rev. 2019 Nov 15;8:281.
36. Glass J, Lanctot KL, Herrmann N, *et al.* Sedative Hypnotics in Older People with Insomnia: Meta-Analysis of Risks and Benefits. BMJ. 2005;331(7526):1169.
37. National Institute for Health and Care Excellence. Bipolar disorder: Assessment and management [Internet]. [London]: NICE; 2014 [updated 2020 Feb; cited 2022 Feb 3]. (Clinical guideline [CG185]). Available from: https://www.nice.org.uk/guidance/cg185.
38. Taylor DM, Barnes TR, Young AH. The Maudsley Prescribing Guidelines in Psychiatry. 14th edition. Chichester, West Sussex. Hoboken, NJ; John Wiley & Sons; 2021.
39. Hedya SA, Avula A, Swoboda HD. Lithium Toxicity. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 [cited 2022 Feb 3]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK499992/

40. Post RM, Weiss SRB. Kindling and manic-depressive illness. In: The Clinical Relevance of Kindling. Oxford, England: John Wiley & Sons; 1989. p. 209-30.
41. Oya K, Sakuma K, Esumi S, *et al.* Efficacy and Safety of Lithium and Lamotrigine for the Maintenance Treatment of Clinically Stable Patients with Bipolar Disorder: A Systematic Review and Meta-Analysis of Double-blind, Randomized, Placebo-Controlled Trials with an Enrichment Design. Neuropsychopharmacol Rep. 2019 Sep;39(3):241-6.
42. Bahji A, Ermacora D, Stephenson C, *et al.* Comparative Efficacy and Tolerability of Adjunctive Pharmacotherapies for Acute Bipolar Depression: A Systematic Review and Network Meta-Analysis. Can J Psychiatry Rev Can Psychiatr. 2021 Mar;66(3):274-88.
43. Yee CS, Vázquez GH, Hawken ER, *et al.* Long-Term Treatment of Bipolar Disorder with Valproate: Updated Systematic Review and Meta-analyses. Harv Rev Psychiatry. 2021 Jun 1;29(3):188-95.
44. Epstein T, Patsopoulos NA, Weiser M. Immediate-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults. Cochrane Database Syst Rev. 2014(9):CD005041.
45. Keam S, Walker MC. Therapies for narcolepsy with or without cataplexy: Evidence-based review. Curr Opin Neurol. 2007;20(6):699-703.
46. Elliott J, Johnston A, Husereau D, *et al.* Pharmacologic Treatment of Attention Deficit Hyperactivity Disorder in Adults: A Systematic Review and Network Meta-Analysis. PLoS ONE. 2020 Oct 21;15(10):e0240584.
47. Barry CL, Martin A, Busch SH. ADHD medication use following FDA risk warnings. J Ment Health Policy Econ. 2012;15(3):119-25.
48. Stanilla JK, Simpson GM. Drugs to treat extrapyramidal side effects. In: The American Psychiatric Association Publishing Textbook of Psychopharmacology. 5th ed. Arlington, VA: American Psychiatric Publishing; 2017.
49. Hornyak M, Scholz H, Kohnen R, *et al.* What treatment works best for restless legs syndrome? Meta-analyses of dopaminergic and nondopaminergic medications. Sleep Med Rev. 2014;18(2):153-64.
50. Sami MB, Faruqui R. The effectiveness of dopamine agonists for treatment of neuropsychiatric symptoms post brain injury and stroke. Acta neuropsychiatrica. 2015 Dec; 27(6):317-26.
51. Azhar L, Kusumo RW, Marotta G, *et al.* Pharmacological Management of Apathy in Dementia. CNS Drugs. 2022 Jan 10:1-23.
52. Barron AJ, Zaman N, Cole GD, *et al.* Systematic review of genuine versus spurious side-effects of beta-blockers in heart failure using placebo control: Recommendations for patient information. Int J Cardiol. 2013;168(4):3572-9.
53. Steenen SA, van Wijk AJ, van der Heijden GJMG, *et al.* Propranolol for the Treatment of Anxiety Disorders: Systematic Review and Meta-Analysis. J Psychopharmacol Oxf Engl. 2016 Feb;30(2): 128-39.
54. Waldon K, Hill J, Termine C, *et al.* Trials of Pharmacological Interventions for Tourette Syndrome: A Systematic Review. Behav Neurol. 2013;26(4):265-73.
55. Weyandt LL, Oster DR, Marraccini ME, *et al.* Pharmacological interventions for adolescents and adults with ADHD: Stimulant and nonstimulant medications and misuse of prescription stimulants. Psychol Res Behav Manag. 2014;7:223-49.
56. Gowing L, Farrell MF, Ali R, *et al.* Alpha2-adrenergic agonists for the management of opioid withdrawal. Cochrane Database Syst Rev. 2014(3):CD002024.
57. Chen LC, Ashcroft DM. Meta-Analysis examining the efficacy and safety of almotriptan in the acute treatment of migraine. Headache. 2007;47(8):1169-77.
58. Tang DH, Malone DC. A network Meta-Analysis on the efficacy of serotonin type 3 receptor antagonists used in adults during the first 24 hours for postoperative nausea and vomiting prophylaxis. Clin Ther. 2012;34(2):282-94.
59. Zheng W, Cai D-B, Zhang Q-E, *et al.* Adjunctive ondansetron for schizophrenia: A systematic review and meta-analysis of randomized controlled trials. J Psychiatr Res. 2019 Jun; 113:27-33.
60. Wang H, Yu J, Tang S, *et al.* Efficacy and Safety of Cholinesterase Inhibitors and Memantine in Cognitive Impairment in Parkinson's Disease, Parkinson's Disease Dementia, and Dementia with Lewy Bodies: Systematic Review with Meta-Analysis and Trial Sequential Analysis. J Neurol Neurosurg Psychiatry. 2015;86(2):135-43.
61. Guaiana G, Barbui C, Cipriani A. Hydroxyzine for generalised anxiety disorder. Cochrane Database Syst Rev. 2010(12):CD006815.
62. Tan CC, Yu JT, Wang HF, *et al.* Efficacy and Safety of Donepezil, Galantamine, Rivastigmine, and Memantine for the Treatment of Alzheimer's Disease: A Systematic Review and Meta-Analysis. J Alzheimers Dis. 2014;41(2):615-31.
63. Folch J, Busquets O, Ettcheto M, *et al.* Memantine for the Treatment of Dementia: A Review on its Current and Future Applications. J Alzheimers Dis JAD. 2018;62(3):1223-40.
64. Donoghue K, Elzerbi C, Saunders R, *et al.* The Efficacy of Acamprosate and Naltrexone in the Treatment of Alcohol Dependence, Europe

Versus the Rest of the World: A Meta-Analysis. Addiction. 2015;
65. Dean O, Giorlando F, Berk M. N-acetylcysteine in psychiatry: Current therapeutic evidence and potential mechanisms of action. J Psychiatry Neurosci JPN. 2011 Mar;36(2):78-86.
66. Yolland CO, Hanratty D, Neill E, *et al.* Meta-Analysis of Randomised Controlled Trials with N-Acetylcysteine in the Treatment of Schizophrenia. Aust N Z J Psychiatry. 2020 May; 54(5):453-66.
67. Kishi T, Miyake N, Okuya M, *et al.* N-Acetylcysteine as an Adjunctive Treatment for Bipolar Depression and Major Depressive Disorder: A Systematic Review and Meta-Analysis of Double-Blind, Randomized Placebo-Controlled Trials. Psychopharmacology. 2020 Nov;237(11):3481-7.
68. Nery FG, Li W, DelBello MP, *et al.* N-Acetylcysteine as an Adjunctive Treatment for Bipolar Depression: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Bipolar Disord. 2021 Nov;23(7):707-14.
69. Nwankwo CO, Jafferany M. N-Acetylcysteine in psychodermatological disorders. Dermatol Ther. 2019 Sep;32(5):e13073.
70. Hoffman J, Williams T, Rothbart R, *et al.* Pharmacotherapy for trichotillomania. Cochrane Database Syst Rev. 2021(9):CD007662.
71. Maiti R, Mishra A, Mishra BR, *et al.* Comparative Efficacy of Mitochondrial Agents for Bipolar Disorder During Depressive Episodes: A Network Meta-Analysis Using Frequentist and Bayesian Approaches. Psychopharmacology. 2021 Dec; 238(12):3347-56.
72. Hadi F, Kashefinejad S, Kamalzadeh L, *et al.* Glutamatergic Medications as Adjunctive Therapy for Moderate to Severe Obsessive-Compulsive Disorder in Adults: A Systematic Review and Meta-Analysis. BMC Pharmacol Toxicol. 2021 Nov 4;22(1):69.
73. Cooper-Kazaz R, Lerer B. Efficacy and safety of triiodothyronine supplementation in patients with major depressive disorder treated with specific serotonin re-uptake inhibitors. Int J Neuropsychopharmacol. 2008;11(5):685-99.
74. Kelly T, Lieberman DZ. The use of triiodothyronine as an augmentation agent in treatment-resistant bipolar II and bipolar disorder NOS. J Affect Disord. 2009;116(3):222-6.
75. Bauer M, Whybrow PC. Role of thyroid hormone therapy in depressive disorders. J Endocrinol Invest. 2021 Nov;44(11):2341-7.
76. Gordon JL, Girdler SS. Hormone replacement therapy in the treatment of perimenopausal depression. Curr Psychiatry Rep. 2014;16(12):517.
77. Dennis CL, Ross LE, Herxheimer A. Oestrogens and progestins for preventing and treating postpartum depression. Cochrane Database Syst Rev. 2008(4):CD001690.
78. Edinoff AN, Odisho AS, Lewis K, *et al.* Brexanolone, a GABAA modulator, in the treatment of postpartum depression in adults: A comprehensive review. Front Psychiatry. 2021;12:699740.
79. Ferracioli-Oda E, Qawasmi A, Bloch MH. Meta-Analysis: Melatonin for the Treatment of Primary Sleep Disorders. PLoS One. 2013;8(5):63773.
80. Glazener CM, Evans JH. Desmopressin for nocturnal enuresis in children. Cochrane Database Syst Rev. 2002(3):CD002112.
81. Espinosa-Jovel C. Cannabinoids in epilepsy: clinical efficacy and pharmacological considerations. Neurol Barc Spain. 2021 Nov 22;S2173-5808(21)00182-6.
82. Black N, Stockings E, Campbell G, *et al.* Cannabinoids for the Treatment of Mental Disorders and Symptoms of Mental Disorders: A Systematic Review and Meta-Analysis. Lancet Psychiatry. 2019 Dec;6(12):995–1010.
83. McGregor IS, Cairns EA, Abelev S, *et al.* Access to cannabidiol without a prescription: A cross-country comparison and analysis. Int J Drug Policy. 2020 Nov;85:102935.
84. Skinner MD, Lahmek P, Pham H, *et al.* Disulfiram Efficacy in the Treatment of Alcohol Dependence: A Meta-Analysis. PLoS One. 2014;9(2):87366.
85. Bhanushali MJ, Tuite PJ. The evaluation and management of patients with neuroleptic malignant syndrome. Neurol Clin. 2004;22(2): 389-411.
86. LaFrance WC Jr, Lauterbach EC, Coffey CE, *et al.* The use of herbal alternative medicines in neuropsychiatry. A report of the ANPA. Comm Res J Neuropsychiatry Clin Neurosci. 2000;12(2):177-92.
87. Sarris J, Panossian A, Schweitzer I, *et al.* Herbal medicine for depression, anxiety and insomnia: A review of psychopharmacology and clinical evidence. Eur Neuropsychopharmacol. 2011; 21(12):841-60.
88. Leichsenring F, Steinert C, Rabung S. The efficacy of psychotherapies and pharmacotherapies for mental disorders in adults: An umbrella review and meta-analytic evaluation of recent meta-analyses. World Psychiatry. 2022 Feb;21(1):133-45.
89. Apaydin EA, Maher AR, Shanman R, *et al.* A systematic review of St. John's wort for major depressive disorder. Syst Rev. 2016 Dec;5(1):148.
90. Birks J, Grimley Evans J. Ginkgo biloba for cognitive impairment and dementia. Cochrane Database Syst Rev. 2009(1):CD003120.
91. Pittler MH, Ernst E. Kava extract for treating anxiety. Cochrane Database Syst Rev. 2003(1):CD003383.
92. Geng J, Dong J, Ni H, *et al.* Ginseng for cognition. Cochrane Database Syst Rev. 2010(12):CD007769.
93. Porst H, Burnett A, Brock G, *et al.* SOP conservative (medical and mechanical) treatment of erectile dysfunction. J Sex Med. 2013;10(1):130-71.

94. Lakhan SE, Vieira KF. Nutritional therapies for mental disorders. Nutr J. 2008;7(1):2.
95. Knuesel T, Mohajeri MH. The role of the gut microbiota in the development and progression of major depressive and bipolar disorder. Nutrients. 2021 Dec 23;14(1):37.
96. Farina N, Isaac MG, Clark AR, *et al.* Vitamin E for Alzheimer's dementia and mild cognitive impairment. Cochrane Database Syst Rev. 2012(11):CD002854.
97. Li G, Mbuagbaw L, Samaan Z, *et al.* Efficacy of Vitamin D Supplementation in Depression in Adults: A Systematic Review. J Clin Endocrinol Metab. 2014;99(3):757-67.
98. Li S, Guo Y, Men J, *et al.* The Preventive Efficacy of Vitamin B Supplements on the Cognitive Decline of Elderly Adults: A Systematic Review and Meta-Analysis. BMC Geriatr. 2021 Jun 16;21(1):367.
99. Psiuk D, Nowak E, Cholewa K, *et al.* The potential role of serotonergic hallucinogens in depression treatment. Life. 2021 Jul 29;11(8):765.
100. Varker T, Watson L, Gibson K, *et al.* Efficacy of Psychoactive Drugs for the Treatment of Posttraumatic Stress Disorder: A Systematic Review of MDMA, Ketamine, LSD and Psilocybin. J Psychoactive Drugs. 2021 Mar;53(1):85-95.

3: Classifying Psychiatric Disorders

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Psychiatric disorders in the DSM-5 and ICD-11 are classified into broad categories, including the depressive disorders (e.g., major depressive disorder), the anxiety disorders (e.g., panic disorder, social anxiety disorder, generalised anxiety disorder), obsessive-compulsive and related disorders (e.g., obsessive-compulsive disorder), trauma- and stressor-related disorders (e.g., post-traumatic stress disorder), sleep-wake disorders (e.g., insomnia disorder, narcolepsy, restless legs syndrome), the schizophrenia spectrum and other psychotic disorders, the neurocognitive disorders (e.g., Alzheimer's disease), and neurodevelopmental disorders (usually first diagnosed in childhood, e.g., attention-deficit/hyperactivity disorder, autism spectrum disorder and intellectual disability).

In this volume, we provide pharmacotherapy approaches to the following psychiatric disorders:

- Major depressive disorder
- Panic disorder and social anxiety disorder
- Generalised anxiety disorder
- Obsessive-compulsive and related disorders
- Post-traumatic stress disorder
- Insomnia disorder
- Schizophrenia
- Bipolar disorder
- Alzheimer's disease
- Attention-deficit/hyperactivity disorder

Each of these disorders is diagnosed according to specific criteria. ICD-11 diagnostic guidelines are supplied in the relevant chapters of this volume. We strongly encourage clinicians to use these diagnostic guidelines to make diagnoses and identify target symptoms for pharmacotherapy and psychotherapy. Although most psychopharmacology research has employed DSM diagnostic criteria, ICD-11 diagnostic guidelines have been developed for use by non-specialists working around the globe and so have several advantages (e.g. avoidance of pseudo-precision).

MAJOR DEPRESSIVE DISORDER

The mood disorders include major depressive disorder (often abbreviated to major depression) and persistent depressive disorder (previously known as dysthymia, a more chronic and less severe form of depression). These are amongst the most prevalent of psychiatric disorders. They are characterised by disturbances in mood and/or loss of interest or pleasure in activities.

It is important to be cognizant of several different aspects of the presentation when diagnosing major depression. These include severity (mild/moderate/severe), the presence of psychotic features (which may be mood-congruent or mood-incongruent), whether there is partial or full remission, and whether several other specifiers apply. These include major depressive disorder with atypical features (characterised by increased eating, increased sleep, mood reactivity), with melancholic features (accompanied by lack of reactivity to pleasurable stimuli, terminal insomnia, significant weight loss and excessive or inappropriate guilt). Also included are seasonal pattern (typically depression that worsens in winter), with anxiety symptoms (where anxious mood or symptoms are prominent), with panic attacks (where ruminations and anxiety-provoking cognitions lead to panic attacks), with mixed features (features of depression and mania or hypomania) and with peripartum onset (i.e. during pregnancy, or within approximately four weeks post-delivery). These distinctions may have implications for pharmacotherapy (see Chapter 5).

It is also important to take a history of previous episodes of mania and hypomania (a less severe form of mania) in all patients who present with major depression to exclude a diagnosis of bipolar disorder. The pharmacotherapy of the depressed phase of bipolar disorder (see Chapter 12) differs significantly from that of unipolar major depression.

ANXIETY DISORDERS

The anxiety disorders include panic disorder, social anxiety disorder (social phobia) and generalised anxiety disorder. Post-traumatic stress disorder and obsessive-compulsive disorder have been classified in separate chapters. It is not always realised that this group of anxiety and related disorders is in fact one of the most prevalent of all psychiatric disorders.[1] There is also evidence that these disorders account for up to one-third of all the costs of psychiatric disorders.[2,3] While disorders such as schizophrenia account for significant direct costs (e.g., hospitalisation), the anxiety and related disorders have greater indirect costs (e.g., costs of unemployment and marital discord).

In this volume, panic disorder and social anxiety disorder are both covered in a single chapter (see Chapter 6), partly because we hold that the selective serotonin re-uptake inhibitors are the first-line treatment in each of these disorders. We also provide a specific algorithm for generalised anxiety disorder (see Chapter 7), partly because this anxiety disorder is prevalent in primary care settings.

OBSESSIVE-COMPULSIVE AND RELATED DISORDERS

The obsessive-compulsive and related disorders include obsessive-compulsive disorder (OCD), body dysmorphic disorder, hoarding disorder, trichotillomania (hair-pulling disorder) and excoriation (skin-picking) disorder.

We have included obsessive-compulsive disorder (OCD) in a separate chapter (see Chapter 8) to reflect the current diagnostic nomenclature and emphasise the obsessive-compulsive-related disorders that may also respond to standard treatments for obsessive-compulsive disorder.

TRAUMA- AND STRESSOR-RELATED DISORDERS

This is a new chapter in the DSM-5, and includes disorders in which exposure to a traumatic or stressful event is an explicit diagnostic requirement. These disorders include post-traumatic stress disorder (PTSD), acute stress disorder, and adjustment disorders.

This book focuses on the pharmacological treatment of PTSD, which can be conceptualised as an abnormal response to psychological trauma, with symptoms persisting beyond one month.

SLEEP-WAKE DISORDERS

The DSM-5 classification of sleep-wake disorders incorporates disorders which are characterised by problems in the quality, timing and amount of sleep, and that invariably result in daytime distress and impairment. These disorders include insomnia disorder, hypersomnolence disorder, narcolepsy, breathing-related sleep disorders, and restless legs syndrome.

We have focused on insomnia disorder (previously known as primary insomnia), as this is a common condition presenting to primary care.[4,5]

SCHIZOPHRENIA SPECTRUM AND OTHER PSYCHOTIC DISORDERS

The psychotic disorders include schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, and brief psychotic disorder. These are all characterised by loss of contact with reality, whether in hallucinations or delusions, and are often accompanied by disorganised speech and behaviour.

Although psychotic episodes are frequently treated in an inpatient setting, identification and follow-up of these patients in South Africa frequently occurs at the primary care level. We have therefore included a chapter on the treatment of schizophrenia.

BIPOLAR AND RELATED DISORDERS

Bipolar and related disorders are separated from the depressive disorders in DSM-5, and placed between chapters on schizophrenia spectrum disorders and depressive disorders, to emphasise the commonalities across these three groups of conditions in terms of symptoms, family histories and genetics.

The main focus of the chapter in this volume is on the acute and chronic management of bipolar I disorder (characterised by at least one episode of mania) and bipolar II disorder (characterised by at least one depressive and one hypomanic episode).

NEUROCOGNITIVE DISORDERS

The cognitive disorders include delirium, major and mild neurocognitive disorder (NCD), and their aetiological subtypes (including but not limited to Alzheimer's disease, vascular disease, traumatic brain injury, substance/medication-induced disorder, HIV infection, Parkinson's disease and Huntington's disease). The term "dementia" has been subsumed under "major

neurocognitive disorder", although it may still be used in aetiological subtypes where it has become standard.

Advances in our understanding of Alzheimer's disease have been particularly exciting. Indeed, several new agents have been introduced specifically for this condition and have subsequently been shown to have efficacy in other neurocognitive disorders.[6-8] Thus, we provide a separate algorithm for Alzheimer's disease (see Chapter 13).

NEURODEVELOPMENTAL DISORDERS

Neurodevelopmental disorders are usually diagnosed first in childhood and include intellectual disability, autism spectrum disorder, attention-deficit/hyperactivity disorder and tic disorders.

Attention-deficit/hyperactivity disorder is important to diagnose as it is associated with significant subsequent morbidity (including substance abuse, unemployment and involvement in criminal activity) and there is effective and safe medication treatment available.[9] We therefore provide an algorithm (see Chapter 14) for this disorder.

REFERENCES

1. Steel Z, Marnane C, Iranpour C, *et al.* The Global Prevalence of Common Mental Disorders: A Systematic Review and Meta-Analysis 1980-2013. Int J Epidemiol. 2014;43(2):476-93.
2. Haller H, Cramer H, Lauche R, *et al.* The Prevalence and Burden of Subthreshold Generalised Anxiety Disorder: A Systematic Review. BMC Psychiatry. 2014;14(1):128.
3. Greenberg PE, Sisitsky T, Kessler RC, *et al.* The economic burden of anxiety disorders in the 1990s. J Clin Psychiatry. 1999;60(7):427-35.
4. Pigeon WR. Diagnosis, prevalence, pathways, consequences & treatment of insomnia. Indian J Med Res. 2010;131:321-32.
5. Ford ES, Wheaton AG, Cunningham TJ, *et al.* Trends in outpatient visits for insomnia, sleep apnea, and prescriptions for sleep medications among US adults: Findings from the National Ambulatory Medical Care survey 1999-2010. Sleep. 2014;37(8):1283-93.
6. He Y, Li H, Huang J, *et al.* Efficacy of Antidepressant Drugs in the Treatment of Depression in Alzheimer Disease Patients: A Systematic Review and Network Meta-Analysis. J Psychopharmacol Oxf Engl. 2021 Aug;35(8):901-9.
7. Wang J, Tan L, Wang HF, *et al.* Anti-inflammatory Drugs and Risk of Alzheimer's Disease: An Updated Systematic Review and Meta-Analysis. J Alzheimers Dis. 2015;44(2):385-96.
8. Balázs N, Bereczki D, Kovács T. Cholinesterase inhibitors and memantine for the treatment of Alzheimer and non-Alzheimer dementias. Ideggyogyaszati Szle. 2021 Nov 30;74(11-12):379-87.
9. Bolea-Alamanac B, Nutt DJ, Adamou M, *et al.* Evidence-based guidelines for the pharmacological management of attention deficit hyperactivity disorder: Update on recommendations from the British Association for Psychopharmacology. J Psychopharmacol. 2014;28(3):179-203.

4: Pros and Cons of Algorithms

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A medical algorithm is a step-by-step approach to describing diagnosis or treatment. The algorithms in this handbook invariably begin with diagnosis as step 1, an initial medication as step 3, and then proceed up to step 7 or 8, for patients who prove particularly refractory to standard treatment approaches. The aim of providing algorithms in this volume is to provide a concise, logical, and user-friendly approach to the pharmacotherapy of psychiatric disorders in the primary care context. The algorithms presented assume an adult patient, unless stated otherwise.

In recent years, several clinical practice guidelines for psychiatric disorders have been published, and syntheses of multiple guidelines are also being developed.[1,2] Ideally, such guidelines have several characteristics, including reliability, flexibility, clarity, and multidisciplinary input, and they generally aim to reflect an up-to-date synthesis of current research.[3] The algorithms here are not based on formal expert consensus or systematic meta-analyses, but rather on our reading of the literature. Their strength lies not so much in consensus and complexity, but rather, we hope, in their concision, logic and user-friendliness.

BENEFITS OF A CONCISE, LOGICAL, AND USER-FRIENDLY APPROACH

Several authors have emphasised that the development of clinical practice guidelines does not ensure their use by clinicians.[4-6] There are several possible reasons why dissemination of guidelines may not alter clinical practice. Not the least of these may be the complexity and unwieldiness of specialised clinical practice guidelines, particularly from the perspective of users in a primary care setting.[7,8]

Nevertheless, guidelines and algorithms have many values. First, there is the increasing emphasis by professional and consumer bodies on the importance of practising evidence-based medicine. The complexity of decision-making in psychiatry has steadily increased in recent years as a result of the introduction of new medications, the completion of hundreds of clinical trials, and the growth in systematic and anecdotal information about the management of treatment-resistant conditions.[9,10] Algorithms may be able to provide a concise and logical "scaffolding" to approach the practice of evidence-based medicine.[11]

Second, there is increasing emphasis by government- and private funding of healthcare on resource allocation and cost-effectiveness in the practice of medicine. The field of pharmacoeconomics has grown rapidly and increasingly plays a role in the development of clinical practice guidelines.[12,13] Once again, algorithms provide a way of summarising currently available information and specifying appropriate clinical options to minimise wasteful and suboptimal practices.[14] They may be able to provide a quick, step-by-step approach to cost-effective practices, incorporating findings from the latest pharmacotherapy trials, guidelines and pharmacogenomic studies.[14,15]

Third, the development of computer-based decision tools for psychiatric assessment and treatment encourages the formulation of algorithms. Many such programmes are based on logical rules, and these are often most usefully articulated with the aid of flow charts or algorithms.[16] Such rules need to be revised, of course, as new clinical data are gathered and analysed.

LEVELS OF EVIDENCE

Development of an algorithm encourages a rigorous review of the past literature. That is, the development of an algorithm requires the clinician to carefully justify clinical decisions in terms of the existing data. Furthermore, algorithms point to the future. The development of an algorithm provides an important focus on those areas where clinical practice, even

when expert, is not supported by research, and where further research is required.[17,18]

The development of algorithms – and their revision after critical assessment and after the gathering and analysis of new data – are arguably useful didactic and research tools. Nevertheless, all algorithms need to be applied with good clinical judgement. Evidence-based psychiatry needs to be integrated with values-based practice, as exemplified by shared decision-making.[19,20] While algorithms can provide a useful overview, they may also run the risk of oversimplification.[21] Simple algorithms may, for example, be irrelevant in patients with complex comorbid psychiatric and medical conditions. Algorithms are intended to provide a "scaffolding" rather than to regulate or automate the practice of medicine.

Certainly, algorithms will never replace the individual clinician; only an experienced and competent decision-maker is able to apply an algorithm in the clinic.[22,23]

REFERENCES

1. Saddichha S, Chaturvedi SK. Clinical practice guidelines in psychiatry: More confusion than clarity? A critical review and recommendation of a unified guideline. ISRN Psychiatry. 2014 Mar 31;2014:1-8.
2. Gabriel FC, de Melo DO, Fráguas R, *et al.* Pharmacological Treatment of Depression: A Systematic Review Comparing Clinical Practice Guideline Recommendations. PloS One. 2020;15(4):e0231700.
3. Maaløe N, Ørtved AMR, Sørensen JB, *et al.* The injustice of unfit clinical practice guidelines in low-resource realities. Lancet Glob Health. 2021 Jun;9(6):e875-9.
4. Cabana MD, Rand CS, Powe NR, *et al.* Why don't physicians follow clinical practice guidelines? A framework for improvement. JAMA. 1999 Oct 20;282(15):1458.
5. Moore TA. Schizophrenia treatment guidelines in the United States. Clin Schizophr Relat Psychoses. 2011;5(1):40-9.
6. Cases C, Gallini A, Lafont Rapnouil S, *et al.* Developing and testing a local expert-based reading process for use to examine discrepancies between guidelines and current clinical practices. Front Psychiatry. 2021;12:581449.
7. Ferenchick EK, Ramanuj P, Pincus HA. Depression in primary care: Part 1 – screening and diagnosis. BMJ. 2019 Apr 8;l794.
8. Ramanuj P, Ferenchick EK, Pincus HA. Depression in primary care: Part 2 – management. BMJ. 2019 Apr 8;l835.
9. Glick ID, Balon RJ, Ballon J, *et al.* Teaching pearls from the lost art of psychopharmacology. J Psychiatr Pract. 2009 Sep;15(5):423-6.
10. Taylor P. Clinical decision making: From theory to practice. JAMA J Am Med Assoc. 1996 Nov 6;276(17):1445.
11. Norra C, Ueberberg B, Juckel G. A new electronically based clinical pathway for schizophrenia inpatients: A longitudinal pilot study. Schizophr Res. 2021 Dec;238:82-90.
12. Weinstein MC, Siegel JE, Gold MR, *et al.* Recommendations of the panel on cost-effectiveness in health and medicine. JAMA. 1996 Oct 16;276(15):1253-8.
13. Development of methodological standards in CNS pharmacoeconomic research: Report of an ACNP Task Force. Neuropsychopharmacology. 2001 Nov;25(5):621-3.
14. Carrascal-Laso L, Franco-Martín MÁ, Marcos-Vadillo E, *et al.* Economic Impact of the application of a precision medicine model (5SPM) on psychotic patients. Pharmacogenomics Pers Med. 2021;14:1015-25.
15. Jašović-Gašić M, Dunjic-Kostić B, Pantović M, *et al.* Algorithms in psychiatry: State of the art. Psychiatr Danub. 2013 Sep;25(3):280-3.
16. Stein DJ, Patterson R, Hollander E. Expert systems for psychiatric pharmacotherapy. Psychiatr Ann. 1994 Jan;24(1):37-41.
17. Möller H-J, Maier W. Evidence-based medicine in psychopharmacotherapy: Possibilities, problems and limitations. Eur Arch Psychiatry Clin Neurosci. 2010 Feb;260(1):25-39.
18. Möller H-J. How close is evidence to truth in evidence-based treatment of mental disorders? Eur Arch Psychiatry Clin Neurosci. 2012 Jun;262(4):277-89.
19. Fulford KWM. Values-based practice: A new partner to evidence-based practice and a first for psychiatry? Mens Sana Monogr. 2008 Jan; 6(1):10-21.
20. Slade M. Implementing shared decision making in routine mental health care. World Psychiatry. 2017 Jun;16(2):146-53.
21. Jakovljevic M. Myths and facts in contemporary psychopharmacotherapy: Evidence-based vs. evidence-biased treatment algorithms practice. Psychiatr Danub. 2007;19(4):342-9.
22. Schünemann HJ, Wiercioch W, Brozek J, *et al.* GRADE evidence to decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. J Clin Epidemiol. 2017 Jan;81:101-10.
23. Stahl SM. Does evidence from clinical trials in psychopharmacology apply in clinical practice? J Clin Psychiatry. 2001 Jan;62(1):6-7.

5: Major Depressive Disorder

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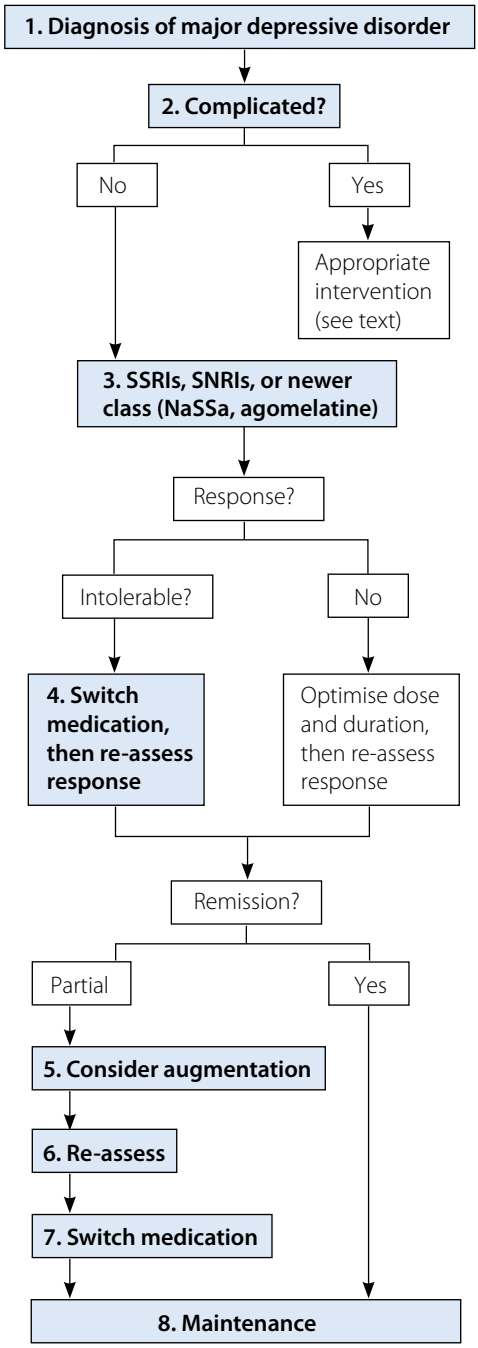
An algorithm for the pharmacotherapy of depression is presented in Figure 5.1. Each line of the algorithm is briefly explained below. It is crucial to state at the outset, however, that psychotherapy is often a useful treatment of depression, either alone or in conjunction with antidepressant medication.[1-3] Similarly, psycho-education about depression may be an important adjunct to both pharmacotherapy and psychotherapy.[4] Organisational strategies and collaborative care models within primary care settings can also contribute to the improved recognition and treatment of depression.[5] The question of whether severity of symptoms should influence the decision of whether to initiate pharmacotherapy, psychotherapy, or their combination remains controversial,[1] although there is some evidence that pharmacotherapy is more efficacious in patients with more severe symptoms.[6]

The algorithm here focuses on major depression. However, there is increasing recognition that persistent depressive disorder (dysthymia) also responds to standard antidepressant treatments.[7-9] This disorder, characterised by chronic depressive symptoms, has significant associated morbidity when left untreated. It therefore also deserves attention

Figure 5.1. Algorithm for pharmacotherapy of depression



from both clinicians and researchers.

The algorithm here also assumes that the patient is an adult. In children and adolescents, selective serotonin re-uptake inhibitors (SSRIs) are better tolerated and more effective than tricyclic antidepressants (TCAs)[10], with the SSRI fluoxetine perhaps being more effective in adolescents.[11] Sertraline, escitalopram and duloxetine may also be considered as options for this age group.[12] Despite their usefulness in treating depression, it is important to note that antidepressants may be associated with an increased risk of suicidal ideation and behaviour in children and adolescents.[12,13] Specialist consultation, if available, is therefore advisable in younger patients.

STEP 1: DIAGNOSIS OF MAJOR DEPRESSIVE DISORDER

Depression should be diagnosed using specific diagnostic guidelines, as outlined in ICD-11 (see Table 5.1.). A range of practical questionnaires that incorporate these criteria is available to help clinicians identify and diagnose patients with major depression.[14-17] Particular attention should be paid by the clinician to symptoms that are chosen as targets for pharmacotherapy. These include mood symptoms, associated symptoms such as pain, and the degree of symptom-related disability. It should be stressed that current evidence indicates that depression remains significantly under-recognised in primary care settings.[18-21]

By definition, major depressive disorder is not diagnosed when there is a history of manic or hypomanic episodes. Rather, patients with such a history are diagnosed with a bipolar disorder. Postpartum depressive episodes are often on the bipolar spectrum.[22,23] It is particularly important to exclude a history of mania or hypomania in patients with a family

Table 5.1. Diagnostic guidelines for depressive episode*

1. Five (or more) of the following characteristic symptoms have been present for most of the day, nearly every day during a period lasting at least two weeks and represent a change from previous functioning; at least one of the symptoms is from the affective cluster.	
A. Affective cluster	• Depressed mood most of the day, nearly every day, as reported or observed. This may be experienced and expressed as irritability, particularly in children or adolescents. • Markedly diminished interest or pleasure in activities, especially those normally found to be enjoyable to the individual.
B. Cognitive-behavioural cluster	• Diminished ability to think or concentrate, or indecisiveness. • Feelings of worthlessness or excessive and inappropriate guilt, which may be delusional. • Hopelessness about the future. • Recurrent thoughts of death, recurrent suicidal ideation, or evidence of suicide attempt.
C. Neurovegetative cluster	• Significantly disrupted sleep (insomnia or hypersomnia). • Significant change in appetite or weight (increase or decrease). • Psychomotor agitation or retardation. • Fatigue, loss of energy or marked tiredness following expenditure of only a minimum of effort.
2. The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning. If function is maintained, it is only through significant additional effort.	
3. The symptoms are not due to the direct physiological effects of a substance (or withdrawal) or a general medical condition.	
4. The symptoms are not better accounted for by bereavement.	
5. The clinical presentation does not fulfil the diagnostic requirements for a mixed episode.	

*Adapted from ICD-11

history of bipolar disorder. The treatment of depression in bipolar disorder is not discussed further here, although atypical antipsychotics and mood-stabilising agents (rather than antidepressants) are the essential ingredients of its treatment.[24-26]

The differential diagnosis of depression includes not only other psychiatric disorders, but also mood disorders due to general medical conditions and substance-induced mood disorders. Most of these disorders can readily be excluded by a thorough medical history, physical examination, and routine blood and urine tests.[19] At the same time, it is also important to be aware of the comorbidity between depression and general medical disorders[27,28], with increasing evidence that depression contributes to the morbidity and mortality of illnesses such as diabetes and coronary artery disease.[29-34]

STEP 2: COMPLICATIONS IN DIAGNOSIS IMPACTING PHARMACOTHERAPY

Depression may be characterised in several ways, impacting decisions about pharmacotherapy and other interventions. Brief explanations of these various complicating features and their implications for pharmacotherapy follow:

a. **Melancholia:** Melancholic features of depression include loss of pleasure in activities, lack of reactivity to pleasurable stimuli, and various neurovegetative symptoms, such as exacerbation of depression in the morning, early-morning awakening, and significant weight loss.[35] Patients with melancholia appear to respond better to antidepressants and electroconvulsive therapy (ECT) and less favourably to psychotherapy and placebo than do non-melancholic patients.[36-38] There is some evidence that patients with melancholic features of depression respond better to older drugs, such as TCAs and mono-amine oxidase inhibitors (MAOIs) than to SSRIs, although not all evidence is consistent.[36,39,40]

b. **Psychotic features:** Clinicians should be alert for psychotic symptoms in depression, as these are sometimes quite subtle. Depression with psychotic features is associated with increased risks for suicide and for recurrent depression. Most authorities hold that it is important to use an antipsychotic agent in addition to an antidepressant in order to achieve an optimal response.[41-43] ECT can also be highly effective, and may also be considered as a first-line treatment for depressed patients with psychotic features.[37,44,45]

c. **'Atypical' features:** These include mood reactivity, as well as neurovegetative symptoms of reversed polarity (i.e., increased rather than decreased sleep and appetite), severe lack of energy or leaden feelings in the limbs (leaden paralysis), and pathologic sensitivity to interpersonal rejection. Patients may present with only some of these symptoms. Classical MAOIs, such as phenelzine, are probably more effective than TCAs in atypical depression.[46] However, in view of the inconvenience caused by dietary and other restrictions when using these agents, SSRIs may be considered a first-line class of medication for these patients.[47,48]

d. **Seasonal affective disorder:** Seasonal affective disorder is a subtype of depression where there is a regular temporal relationship between season (usually autumn/winter) and depression, which cannot be accounted for by seasonal stressors. Seasonal affective disorder has been shown to respond to light therapy, as well as to antidepressant drugs.[49] Symptoms of depression are often atypical rather than typical, and SSRIs may also be considered as a first-line treatment.[50]

e. **Comorbid anxiety or anxiety disorders:** Comorbidity of depression and anxiety is extremely common, and is associated with more severe and treatment-refractory depression.[51,52] In patients with depression and a high level of anxiety, short-term augmentation of an antidepressant with a benzodiazepine may reduce distress and increase adherence.[53] In patients with depression and comorbid panic disorder, it is often useful to begin at lower doses of antidepressants than usual in view of the fact that anxiety symptoms are often initially exacerbated at ordinary doses. The use of a serotonin re-uptake inhibitor (i.e., clomipramine or one of the SSRIs) is advised in patients with depression and comorbid obsessive-compulsive disorder. SSRIs or the serotonin-noradrenaline re-uptake inhibitor (SNRI) venlafaxine are advisable in patients with depression and comorbid social anxiety disorder, rather than TCAs.

f. **Alcohol and/or substance use:** Depression and substance-use disorder are often

comorbid. For this reason, a detailed history of substance abuse is essential in patients with depression. Depressed patients with comorbid substance-use disorders are more likely to require hospitalisation, more likely to attempt suicide, and less likely to adhere to treatment.[54] However, abstinence may itself lead to some improvement in symptoms of depression. It may therefore be advisable to detoxify patients prior to beginning antidepressant treatment.[55] On the other hand, a positive family history of depression, a history of depression preceding alcohol- or other substance use, or a history of major depression during periods of sobriety raises the possibility that early intervention with antidepressants may be useful. These may be combined with a drug to prevent alcohol relapse, such as naltrexone.[56]

g. **Suicide:** In patients with suicidal ideation, it is important to consider whether pharmacotherapy should be initiated in hospital or under close supervision.[57] Remember also that the risk of suicide in some patients recovering from depression may increase transiently as they develop the energy and capacity to act on self-destructive plans made earlier in the course of their illness.[58] If suicidal patients are treated as outpatients, it may be advisable to favour medications that have higher safety in overdose (such as the SSRIs). If TCAs are used in this setting, it is advisable to prescribe only limited amounts of medication (no more than a one-week supply).

h. **Pregnancy, lactation, and menopause:** Depression during pregnancy should be treated by non-pharmacotherapeutic interventions whenever possible. However, where clinical considerations outweigh the potential risks of medication, one of the SSRIs may be considered in consultation with a specialist. Adverse pregnancy outcome studies can be difficult to interpret and it is not always clear whether outcomes observed are due to medications themselves or confounders such as the underlying mental illness.[59] SSRIs are generally considered safe first-line agents in pregnancy and there is currently no conclusive evidence of an association between treatment with these agents and increased risk for malformations, preterm birth, low birth weight or small-for-gestational-age births.[60] However, fluoxetine and paroxetine use in early pregnancy may be associated with a small increased risk for cardiovascular malformations. Initiation of these agents should therefore be avoided in the first trimester.[60] The risk of persistent pulmonary hypertension of the newborn has been shown to be increased for infants exposed to SSRIs (particularly paroxetine) in late pregnancy, although clinically the absolute risk is low.[61] ECT is both safe and effective for treatment of depression in pregnancy. It may be used in selected cases, or in patients where depression is complicated by psychotic features.[62-64]

There is some evidence for the efficacy of antidepressants in postpartum depression,[65] and antidepressants can also be used prophylactically in patients with a history of this condition.[66] There is also good evidence for the use of brexanolone as an antidepressant agent in postpartum depression, although this is not locally available.[67] Depression during lactation should again be treated by non-pharmacotherapeutic interventions when possible. There is some evidence for the safety of SSRIs and SNRIs during lactation[68,69], although even here there is some passage of drug and metabolites to the breastfeeding infant. Sertraline has the lowest relative dose passed on to the infant, but expert recommendation is that the same SSRI to which the patient has responded should be continued.[68,70] Specialist consultation should again be sought prior to using medication in this context. Depression may be exacerbated in susceptible patients during menopause, and hormone replacement therapy may sometimes be considered as an adjunct to standard pharmacotherapy.[71,72]

i. **Comorbid medical disorders and medications:** Antidepressants are effective in a wide range of general medical disorders with comorbid major depression.[27] However, clinicians and patients need to be aware of the multiple interactions between antidepressants and other medications.[73,74] In addition, specific medical disorders in patients with depression may impact the choice of antidepressant medication.

Cardiac disease: TCAs are contra-indicated in a number of cardiac conditions, including ventricular arrhythmia, subclinical sinus node dysfunction, conduction defects

(including asymptomatic conduction defects), prolonged QT-intervals, and a recent history of myocardial infarction.[75,76] Although a number of the SSRIs appear to be safe for patients with pre- and existing cardiac disease[77], both citalopram and escitalopram are associated with a dose-dependent QTc- prolongation.[78,79] A depressed patient with a history of any cardiac disorder should be monitored for the emergence of cardiac symptoms, ECG changes, and orthostatic blood pressure decrements. Consultation with a cardiologist before and during anti-depressant treatment may be advisable.[75]

Stroke: The onset of depression in the post-stroke period is common[80], and perhaps unrelated to anatomical location of the lesion.[81,82] Although the literature is uncertain regarding treatment of post-stroke depression, there is some evidence for the value of antidepressants in this context, reducing impairment following stroke.[83,84]

Epilepsy: Many antidepressants lower the seizure threshold and theoretically exert an adverse effect on seizure control in depressed patients with epilepsy. Although TCAs can still be used in such patients, the initial dosages should be lower than usual and subsequent dosage increases should be gradual. Bupropion is contra-indicated in patients with a seizure disorder. The preferred drugs for treating depression in the context of epilepsy are the SSRIs, which themselves may possess anti-epileptic properties.[85,86] Epilepsy is not a contra-indication to ECT.

Glaucoma/obstructive uropathy/etc: Anti-cholinergic effects of the TCAs are undesirable in a number of settings. TCAs may, for example, precipitate acute narrow-angle glaucoma in susceptible individuals (i.e., those with shallow anterior chambers). Prostatism and other forms of bladder outlet obstruction are relative contraindications to the use of TCAs. Anticholinergic antidepressants may also exacerbate memory problems in patients with central nervous disorders, such as Parkinson's disease or dementia.[87]

STEP 3: FIRST-LINE PHARMACOTHERAPY

Most guidelines recommend that any one of the different antidepressants can be used as a first-line treatment in uncomplicated patients with major depressive disorder.[1,5,88,89] There is now a good deal of experience not only with older medications, such as the TCAs and SSRIs/SNRIs, but also with newer agents, such as agomelatine and vortioxetine. Evidence of superior efficacy of one class of antidepressants is inconclusive.[11,90] There is some evidence that SNRIs have an advantage over SSRIs, but this does not appear clinically significant,[91] and there is also some evidence that SSRIs may outperform SNRIs.[90] Similarly, it is probably premature to conclude that any of the currently available antidepressants definitely have a more rapid onset of effect.[92,93] Thus, for now, the choice between antidepressant agents is primarily made on the basis of tolerability, side effects and cost.[5,94]

SSRIs are particularly useful as a first-line treatment in view of their established efficacy and tolerable side-effect profile, a point made in several practice guidelines.[5,43,95,96] Prescription of therapeutic dosages is typically straightforward and side effects and adverse events can be minimised by starting at the lowest available dose.[97,98] The SSRIs, compared to TCAs, appear relatively safe in overdose.[98] SSRIs may be particularly helpful in younger patients and perhaps the elderly, where side effects of older antidepressants can be problematic.[10,11,99,100]

Venlafaxine, desvenlafaxine and duloxetine (SNRIs), reboxetine (a noradrenergic re-uptake inhibitor, or NARI), mirtazapine (a noradrenergic and specific serotonergic antidepressant, or NaSSA), bupropion (a noradrenergic and dopaminergic re-uptake inhibitor), agomelatine (a melotonergic antidepressant), and vortioxetine (a "multimodal" and predominantly serotonergic drug), are also useful first-line options for the treatment of major depression.

Venlafaxine is predominantly a serotonin re-uptake blocker at lower doses and a combined serotonin/norepinephrine re-uptake blocker at higher doses; this profile may contribute to its apparently superior effect on the remission of symptoms, but also to an increased side-effect burden and adverse reactions.[90,101] Desvenlafaxine, a synthetic form of the major active metabolite of venlafaxine, has recently become available on the South African market.

Mirtazapine is an α2-noradrenergic antagonist (increasing noradrenergic and serotonergic transmission) and a 5HT2 and 5HT3 antagonist. This unique mode of action is associated with a useful range of clinical effects and side effects (e.g., increased sedation, fewer

sexual side effects) and may have a more rapid onset of action during initial treatment.[102]

Bupropion, a norepinephrine and dopamine re-uptake inhibitor (NDRI), is an antidepressant that is also marketed for decreasing the craving associated with smoking cessation, and it is relatively free from sexual side effects.[103-105]

Agomelatine is a melatonin receptor agonist and 5HT2 receptor antagonist that is effective and well-tolerated in depression (with minimal effects on weight or sexual functioning), and may be particularly useful for patients who have intolerable side effects on SSRIs or SNRIs.[106]

Vortioxetine is a multimodal antidepressant with a unique mechanism of action and proven efficacy for the treatment of major depressive disorder.[107] Meta-analyses suggest it may have a favourable combination of efficacy and tolerability through its effects on multiple serotonin receptors and re-uptake inhibition.[108]

TCAs have long been used in the treatment of depression and likely work as quickly and with similar efficacy to the new-generation antidepressants. However, clinicians often prescribe subtherapeutic dosages of these agents, due to intolerable side effects and cardiac conduction concerns at higher doses.[95] The TCAs are also unsafe in overdose. On the other hand, low doses can be therapeutic for some patients[109] and some TCAs (e.g., the secondary tricyclics) have relatively favourable side-effect profiles[110] – therefore these agents remain an option, even in the elderly.[100,111]

Extracts of St John's Wort *(Hypericum perforatum)* can be an effective and generally well-tolerated treatment for depression and may be a useful option in patients who refuse conventional medication, particularly when depression levels are only mild to moderate.[112] However, the precise mechanism of action is unknown, and the majority of preparations are neither standardised nor licensed. Furthermore, St John's Wort is involved in a number of drug interactions, resulting in lower plasma concentrations of various other drugs, including antiretrovirals, digoxin, warfarin and oral contraceptives:[112,113] The combination with SSRIs may result in serotonin syndrome. Various other herbals or nutraceuticals (e.g., tryptophan, 5-hydroxytryptophan, omega-3 fatty acids, vitamin D, and magnesium) have some evidence for efficacy, but cannot be supported as first-line agents.[114-116] The older, irreversible MAOIs (such as phenelzine), which require specific dietary restrictions, are no longer used as first-line agents.

In recent years, there has been growing interest in the use of serotonergic psychedelics, such as psilocybin, lysergic acid diethylamide (LSD) and methylenedioxy-N-methamphetamine (MDMA) as treatment for depression. Some studies have shown beneficial effects of psychedelics in reducing symptoms of depression.[117-119] Despite showing some potential as novel treatments for depression, further research is needed to establish their efficacy and safety as therapeutic modalities.[120] Similarly, the evidence for the use of cannabinoids in the treatment of mood disorders is still limited, and there are concerns regarding their potential to precipitate or exacerbate psychotic symptoms.[121,122]

Several other factors may also influence the choice of agent. Agents that have proved efficacious and tolerable in a particular individual in the past should be favoured in the present. Similarly, a family history of response to a particular antidepressant may favour the choice of that agent.[1,123,124] Patient preference for a particular agent is often a deciding factor. There is growing literature on pharmacogenomic predictors of antidepressant response, but this has not yet been proven effective or cost-effective in primary care. Similarly, while predictive algorithms are being developed to further aid in the choice of antidepressant medication, these have not yet been shown to have clinical utility in primary care.[125]

An interesting area of current research focuses on interventions to decrease the response time of antidepressants. There are theoretical reasons for suggesting that certain combinations of agents, by combined receptor action, may be able to achieve this result. To date, however, such work has not translated into clinical recommendations,[92] although there is increasing evidence of efficacy for ketamine and esketamine in rapidly reducing depressive symptoms and suicidal ideation.[126] In this guideline, the use of ketamine as an agent for treatment of depression is discussed briefly under the section on treatment resistance.

Other important aspects of psychoeducation regarding the treatment of depression include imparting the facts that antidepressants are not addictive and side effects that may occur are typically transient. It is important to emphasise to patients that onset of therapeutic response may be delayed, that an adequate trial is warranted before changing to another agent, and that if one agent does not work a different one should be tried.

Continued on page 42

Table 5.2. Montgomery and Asberg depression rating scale

1. Apparent sadness	
Representing despondency, gloom and despair (more than just ordinary, transient low spirits) reflected in speech, facial expression and posture. Rate depth and inability to brighten up.	**0** No sadness **1** **2** Looks dispirited but does brighten up without difficulty **3** **4** Appears sad and unhappy most of the time **5** **6** Looks miserable all the time. Extremely despondent
2. Reported sadness	
Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope. Rate according to intensity, duration and the extent to which the mood is influenced by events.	**0** Occasional sadness in keeping with circumstances **1** **2** Sad or low, but brightens up without difficulty **3** **4** Pervasive feelings of sadness and gloominess. The mood is still influenced by external circumstances **5** **6** Continuous or unvarying sadness, misery or despondency
3. Inner tension	
Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish. Rate according to intensity, duration or extent of reassurance required.	**0** Placid. Only fleeting inner tension **1** **2** Occasional feelings of edginess and ill-defined discomfort **3** **4** Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty **5** **6** Unrelenting dread or anguish. Overwhelming panic
4. Reduced sleep	
Representing the experience of reduced duration or depth of sleep, compared to the subject's own normal pattern when well.	**0** Sleep as usual **1** **2** Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep **3** **4** Sleep reduced or broken by at least two hours **5** **6** Less than two or three hours' sleep
6. Concentration difficulties	
Representing difficulties collecting one's thoughts mounting to incapacitating lack of concentration. Rate according to intensity, frequency and incapacity produced.	**0** No difficulties in concentrating **1** **2** Occasional difficulties in collecting one's thoughts **3** **4** Difficulties in concentration and sustaining thought which reduces ability to read or hold a conversation **5** **6** Unable to read or converse without great difficulty

Table 5.2. (continued)

7. Lassitude	
Representing a difficulty getting started or slowness initiating and performing everyday activities.	**0** Hardly any difficulty getting started. No sluggishness **1** **2** Difficulties in starting activities **3** **4** Difficulties in starting simple activities which are carried out with effort **5** **6** Complete lassitude. Unable to do anything without help
8. Inability to feel	
Representing the subjective experience of reduced interest in the surroundings or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced. Rate according to intensity, duration and the extent to which the mood is influenced by events.	**0** Normal interest in surroundings and in other people **1** **2** Reduced ability to enjoy usual interest **3** **4** Loss of interest in the surroundings. Loss of feelings for friends and acquaintances **5** **6** The experience of being emotionally paralysed, inability to feel anger or grief and a complete or even painful failure to feel for close relatives or friends
9. Pessimistic thoughts	
Representing thoughts of guilt, self-reproach, sinfulness, remorse and ruin.	**0** No pessimistic thoughts **1** **2** Fluctuating idea of failure, self-reproach or self-depreciation **3** **4** Persistent self-accusation or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future **5** **6** Delusions of ruin, remorse or unredeemable sin. Self-accusations which are absurd and unshakeable
10. Suicidal thoughts	
Representing the feeling that life is not worth living, that a natural death would be more welcome, suicidal thoughts and preparations for suicide. Suicide attempts should not in themselves influence the rating.	**0** Enjoys life or takes it as it comes **1** **2** Weary of life. Only fleeting suicidal thoughts **3** **4** Probably better off dead. Suicidal thoughts are common and suicide is considered as a possible solution, but without specific plan of action **5** **6** Explicit plans for suicide when there is an opportunity. Active preparations for suicide
Total score:	**0-6 = normal/symptoms absent** **7-19 = mild depression** **20-34 = moderate depression** **>34 = severe depression**

STEP 4: ASSESS RESPONSE TO TREATMENT

To determine response to medication, it is important to ask about change in those symptoms that were initially targeted for treatment. Side effects of the medication should also be determined, with particular attention to specific side effects that patients may be reluctant to disclose (e.g., sexual dysfunction). To standardise self-reported symptom response to medication, it is useful to have the patient complete a rating scale of depression severity (Table 5.2.).[127] In addition to monitoring depression symptoms, it is important to ascertain overall change in objective disability and subjective wellbeing (i.e., quality of life).

Patients who are intolerant of a particular medication can be switched to another agent. For example, when TCA side effects prove intolerable, it may well be useful to switch to a SSRI. Within the SSRIs, adverse effects may not be seen when an alternative SSRI is used (for example, fluvoxamine has been reported to have a lower risk of sexual side effects).[128] For patients who have specific side effects, such as sexual dysfunction, mirtazapine and bupropion may be useful alternatives.[105]

When there has been a poor response to medication, it is important to optimise antidepressant dosage. Some antidepressants (for example, venlafaxine), show a relationship between dose and response, and between dose and side effects.[129] The steepness of the dose-response curve relationship varies from drug to drug (it is relatively more flat for the SSRIs). In some cases, there is a therapeutic window beyond which increased doses are less effective (e.g., nortriptyline). However, in general, the optimal dosage is as close to the maximum recommended dosage as the patient can tolerate.

As noted earlier, clinicians often prescribe suboptimal doses of antidepressants. This is particularly so in the case of the TCAs, where medications like imipramine and amitriptyline are not typically raised to suggested average doses of 150 to 200 mg daily. Even in the case of the SSRIs, some patients may fail to respond to the standard initial starting dose, but do well at higher doses.[129]

Furthermore, there is increased awareness that some patients may be "rapid metabolisers" of medication and therefore require significantly higher doses than usual.[124] Thus, for example, when patients on TCAs have little response and few anticholinergic side effects on average doses of medication (e.g., imipramine 150-200 mg), it may be useful to further increase dosage while monitoring ECG and perhaps drug levels. Pharmacogenetic profiling may also be relevant in such cases.

Many patients demonstrate a response to medication within the first two weeks of starting treatment. In other patients, this initial response may be delayed for several more weeks.[129] While there is some evidence that patients who have an onset of effect within the first two weeks of treatment are more likely to have a better outcome at eight weeks[95], it is important to give each patient a trial of medication that is of adequate duration (6-8 weeks at a therapeutic dose).

STEP 5: MAINTENANCE OF RESPONSE AND AUGMENTATION STRATEGIES FOR PARTIAL RESPONSE

Patients should be re-assessed at the end of a clinical trial of optimal dosage and duration. Increasingly, the literature emphasises not only a significant reduction in depressive symptoms, but also the value of aiming for symptom remission as well as functional recovery.[130] Patients with reduced but not remitted symptoms may continue to experience significant disability and are at increased risk for relapse.[131]

When the patient has a good response to medication, it is important to reinforce the necessity for continuing the medication at the therapeutic dose despite this improvement. Guidelines for maintenance therapy of depression have become increasingly inclined to recommend longer-term treatment. Modern antidepressant agents are relatively safe, and there is a high likelihood of additional episodes of depression in patients with repeated past episodes.[132] In patients with a single episode of uncomplicated depression, current consensus suggests it is reasonable to continue medication for 9-12 months before gradual tapering (to avoid withdrawal symptoms and to monitor potential relapse).[5,95] Patients with multiple previous episodes, a complicated course or prominent residual symptoms may benefit from maintenance therapy of at least one to three years.[133,134] Risk factors for recurrence include history of multiple episodes, persistent dysthymic symptoms after recovery from major depression, and comorbid psychiatric and medical disorders.[5,130] There is also increased awareness of the potential long-term

adverse effects of antidepressants (insomnia, weight gain, sexual problems), and these require careful monitoring. A combination of pharmacotherapy and psychotherapy may be the most effective form of maintenance therapy.[5,135-137]

Approximately 30% of patients with major depression will not respond to initial treatment, and a further 30% may have only a partial response.[138] When there is a partial response despite an optimum trial of medication, it may be useful to consider an augmenting agent. Even among apparent responders, 'residual symptoms' of depression are common, and, as noted earlier, are associated with a greater likelihood of relapse. There are few controlled studies directly comparing augmentation strategies with switching medications, although both strategies have comparable results.[139]

Augmentation offers the advantage of retaining any possible gains from the first agent, but also carries the potential disadvantages of polypharmacy (more side effects or drug interactions).[140]

There is good evidence from controlled trials that lithium (at serum levels above 0,4 mEq/L) is effective in enhancing the response to TCAs, SSRIs and other second-generation antidepressants.[141,142] An additional advantage of lithium is that it can lower the risk of suicide in patients with mood disorders.[143] The second-generation antipsychotics can also be considered, and are supported by robust evidence[144-146]; however their side-effect profile and poorer tolerability can lead to increased discontinuation rates.[147] The evidence for triiodothyronine (T3) augmentation (doses up to 50 ug/day) is less robust. Despite having been used since the 1960s to improve the response to antidepressants, there is much heterogeneity in clinical trials and it is not clear whether it is an efficacious augmentation strategy for drugs other than TCAs.[138,148,149] Other agents (buspirone, pindolol, dopamine agonists and psychostimulants, anticonvulsants, inositol, opiates, dehydroepiandosterone [DHEA], folate and S-adenosyl-methionine [SAM], and omega-3 fatty acids, N-acetylcysteine) have also been suggested, but the data to date remain anecdotal or conflicting.[150,151] In recent years, there has been an increasing tendency for clinicians to prescribe a second antidepressant from another class that acts on different neurotransmitter systems; for example, combining an SSRI with a noradrenergic agent. Despite some positive findings[152], the evidence for this approach is inconsistent and should not be routinely recommended.[153]

STEP 6: FAILURE TO RESPOND

When a patient with major depressive disorder does not respond to a clinical trial of optimal dose and duration, it is useful to re-assess a number of factors.[154] The presence of certain features may impact on the choice of the subsequent intervention.

a. **Severity:** In patients with a severe major depressive disorder, the need for hospitalisation should be carefully monitored on a continuous basis. In addition, in such patients the need for ECT should be considered. Referral to a specialist may be advisable.
b. **Adherence:** It is not unlikely that clinicians often overestimate the adherence of their patients. Many patients worry that medication is potentially addictive or 'a psychological crutch'[97,114] It is well worth checking with the patient and family whether medication is in fact being taken on a daily basis in a regular way.
c. **Comorbid substance use:** In patients who fail to respond to pharmacotherapy of major depression, the possibility of comorbid substance use should again be considered. There may be a need for the patient to undergo drug detoxification before tackling the depression.
d. **Comorbid personality disorders:** The presence of a comorbid personality disorder may have a negative impact on the course of depression.[155] Although antidepressants may still be useful, additional interventions, such as psychotherapy, may be crucial in patients with depression and comorbid personality disorders. While improvement in depressive symptoms may reduce maladaptive behaviour in some patients with comorbid personality disorder, there are other patients (e.g., those with borderline personality disorder) in whom the personality disorder itself may need to be another priority target of treatment.
e. **Underlying medical disorder:** Depressed patients who fail to respond to medication should be thoroughly re-assessed for an underlying medical disorder. Apathy has been reported as an adverse event of some antidepressant agents and may masquerade as depression.

f. **Pharmacokinetic issues:** Drug-drug interactions may result in a subtherapeutic dose of the prescribed antidepressant.
g. **Psychosocial issues:** Assessment of psychosocial circumstances that continue to complicate the course of a depression need to be assessed, as these may necessitate appropriate intervention.[154]

STEP 7: TREATMENT RESISTANCE

After the failure of an adequate clinical trial of medication in a patient where re-assessment sheds no light on any further unresolved factors, a different antidepressant should be used. Switching between classes of antidepressant has long been considered a useful strategy in non-responders, and there are controlled data to support this idea for certain agents.[138,156] Switching from one SSRI to another may also be useful.[157,158] In most cases, cross-tapering is possible, but drug half-life (e.g., fluoxetine has the longest half-life of the SSRIs) and drug-interactions (e.g., MAOIs should not be overlapped with other antidepressants) should be borne in mind.[159]

Some medications may be particularly useful in cases of depression that do not respond to one or more antidepressants. Although some clinicians no longer use TCAs because of their side-effect profile, these agents continue to have a role. For example, TCAs may be particularly useful in patients with melancholic features[36] and in possibly related subgroups such as inpatients with depression[110], although not all evidence is consistent.[36] High doses of venlafaxine (e.g., up to 375 mg), have been demonstrated to be effective in patients with treatment-resistant depression.[102] There is some evidence for the use of single-dose intravenous racemic ketamine or nasal esketamine in treatment-resistant depression, although further research is needed into the balance of benefit and risk in repeated ketamine treatment.[160]

Furthermore, the classical MAOIs remain a useful resource for patients who have not responded to other more commonly used classes of medication.[46] ECT can be considered[37,161], and other newer but promising non-pharmacological somatic interventions (e.g., transcranial magnetic stimulation, vagus nerve stimulation, deep brain stimulation, trigeminal nerve stimulation, transcranial direct current stimulation) may also have a limited role.[161-163]

Oestrogen augmentation may have a role in perimenopausal/postmenopausal treatment-refractory depression[164] and in postpartum depression.[165] The role of the atypical antipsychotics as augmenting agents in refractory depression is promising.[138,144,146] Indeed, as response to augmentation may not be related to the degree of non-response to the preceding monotherapy trial, augmentation strategies can sometimes be useful in patients who have not responded to multiple single agents.[146,147,159] Although the current algorithms focus on medication treatment, psychotherapy may also have an important role in treatment-resistant depression.[166,167]

ADDITIONAL READING

1. American Psychological Association. (2019). Clinical practice guideline for the treatment of depression across three age cohorts. Retrieved from https://www.apa.org/depression-guideline American Psychiatric Association.
2. Parikh SV, Quilty LC, Ravitz P, *et al.* Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: Section 2. Psychological Treatments. Can J Psychiatry. 2016 Sep;61(9):524-39.
3. Cleare A, Pariante CM, Young AH, *et al.* Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. J Psychopharmacol. 2015 May;29(5): 459-525.
4. National Institute for Health and Care Excellence. Depression in adults: Treatment and management [Internet]. [London]: NICE; 2022. (NICE guideline [NG222]). Available from: https://www.nice.org.uk/guidance/ng222.
5. Von Wolff A, Holzel LP, Westphal A, *et al.* Selective Serotonin Re-Uptake Inhibitors and Tricyclic Anti-Depressants in the Acute Treatment of Chronic Depression and Dysthymia: A Systematic Review and Meta-Analysis. J Affect Disord. 2013; 144 (1-2):7-15.
6. Carvalho AF, Berk M, Hyphantis TN, *et al.* The integrative management of treatment-resistant depression: A comprehensive review and perspectives. Psychother Psychosom. 2014;83(2):70-88.
7. Bridge JA, Iyengar S, Salary CB, *et al.* Clinical Response and Risk for Reported Suicidal Ideation and Suicide Attempts in Pediatric Antidepressant Treatment: A Meta-Analysis of Randomized Controlled Trials. JAMA. 2007;297(15):1683-96.
8. Kessler RC, Sampson NA, Berglund P, *et al.* Anxious and non-anxious major depressive disorder in the World Health Organization World Mental Health Surveys. Epidemiol Psychiatr Sci. 2015:1-17.

9. Apaydin EA, Maher AR, Shanman R, *et al.* A Systematic Review of St. John's Wort for Major Depressive Disorder. Syst Rev. 2016 Sep 2;5(1):148.

REFERENCES

1. Parikh SV, Quilty LC, Ravitz P, *et al.* Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 2. Psychological Treatments. Can J Psychiatry. 2016 Sep;61(9):524-39.
2. Cuijpers P, Sijbrandij M, Koole S, *et al.* Psychological Treatment of Generalized Anxiety Disorder: A Meta-Analysis. Clin Psychol Rev. 2014;34(2):130-40.
3. Cuijpers P, Oud M, Karyotaki E, *et al.* Psychologic Treatment of Depression Compared with Pharmacotherapy and Combined Treatment in Primary Care: A Network Meta-Analysis. Ann Fam Med. 2021;19(3):262-70.
4. Tursi MF, Baes C, Camacho FR, *et al.* Effectiveness of Psychoeducation for Depression: A systematic review. Aust N Z J Psychiatry. 2013;47(11):1019-31.
5. National Institute for Health and Care Excellence. Depression in adults: Treatment and management [Internet]. [London]: NICE; 2022 [cited 2022 Jul 5]. (NICE guideline [NG222]). Available from: https://www.nice.org.uk/guidance/ng222.
6. Fournier JC, DeRubeis RJ, Hollon SD, *et al.* Antidepressant Drug Effects and Depression Severity: A Patient-Level Meta-Analysis. JAMA. 2010;303(1):47-53.
7. von Wolff A, Hölzel LP, Westphal A, *et al.* Selective Serotonin Re-Uptake Inhibitors and Tricyclic Antidepressants in the Acute Treatment of Chronic Depression and Dysthymia: A Systematic Review and Meta-Analysis. J Affect Disord. 2013 Jan 10;144(1-2):7-15.
8. Kriston L, von Wolff A, Westphal A, *et al.* Efficacy and Acceptability of Acute Treatments for Persistent Depressive Disorder: A Network Meta-Analysis. Depress Anxiety. 2014; 31:621-30.
9. Levkovitz Y, Tedeschini E, Papakostas GI. Efficacy of Antidepressants for Dysthymia: A Meta-Analysis of Placebo-Controlled Randomized Trials. J Clin Psychiatry. 2011;72(4):509-14.
10. Qin B, Zhang Y, Zhou X, *et al.* Selective Serotonin Re-Uptake Inhibitors versus Tricyclic Antidepressants in Young Patients: A Meta-Analysis of Efficacy and Acceptability. Clin Ther. 2013; 36:1087-95.
11. Cipriani A, Zhou X, Del Giovane C, *et al.* Comparative Efficacy and Tolerability of Antidepressants for Major Depressive Disorder in Children and Adolescents: A Network Meta-Analysis. The Lancet. 2016 Aug; 388(10047):881-90.
12. Hetrick SE, McKenzie JE, Bailey AP, *et al.* New Generation Antidepressants for Depression in Children and Adolescents: A Network Meta-Analysis. Cochrane Database Syst Rev. 2021(5):CD013674.
13. Boaden K, Tomlinson A, Cortese S, *et al.* Antidepressants in Children and Adolescents: Meta-Review of Efficacy, Tolerability and Suicidality in Acute Treatment. Front Psychiatry. 2020 Sep 2;11:717.
14. Patel JS, Oh Y, Rand KL, *et al.* Measurement invariance of the patient health questionnaire 9 (PHQ 9) depression screener in U.S. adults across sex, race/ethnicity, and education level: NHANES 2005-2016. Depress Anxiety. 2019 Sep;36(9):813-23.
15. Kroenke K, Wu J, Yu Z, *et al.* Patient Health Questionnaire Anxiety and Depression Scale: Initial validation in three clinical trials. Psychosom Med. 2016 Jul;78(6):716-27.
16. Kroenke K, Spitzer RL, Williams JB, *et al.* The Patient Health Questionnaire Somatic, Anxiety, and Depressive Symptom Scales: A Systematic Review. Gen Hosp Psychiatry. 2010;32(4):345-59.
17. Williams JW Jr, Pignone M, Ramirez G, *et al.* Identifying depression in primary care: A literature synthesis of case-finding instruments. Gen Hosp Psychiatry. 2002;24(4):225-37.
18. Costantini L, Pasquarella C, Odone A, *et al.* Screening for Depression in Primary Care with Patient Health Questionnaire-9 (PHQ-9): A Systematic Review. J Affect Disord. 2021 Jan;279:473-83.
19. Schumann I, Schneider A, Kantert C, *et al.* Physicians' Attitudes, Diagnostic Process and Barriers Regarding Depression Diagnosis in Primary Care: A Systematic Review of Qualitative Studies. Fam Pract. 2012 Jun;29(3):255-63.
20. Ferenchick EK, Ramanuj P, Pincus HA. Depression in primary care: Part 1 – screening and diagnosis. BMJ. 2019 Apr 8;l794.
21. Mitchell AJ, Vaze A, Rao S. Clinical Diagnosis of Depression in Primary Care: A Meta-Analysis. Lancet. 2009;374(9690):609-19.
22. Sharma V, Doobay M, Baczynski C. Bipolar postpartum depression: An update and recommendations. J Affect Disord. 2017 Sep;219:105-11.
23. Azorin JM, Angst J, Gamma A, *et al.* Identifying features of bipolarity in patients with first-episode postpartum depression: Findings from the international BRIDGE study. J Affect Disord. 2012;136(3):710-5.
24. Ketter TA, Miller S, Dell'Osso B, *et al.* Balancing benefits and harms of treatments for acute bipolar depression. J Affect Disord. 2014 Dec;169:S24-33.
25. Cerullo MA, Strakowski SM. A systematic review of the evidence for the treatment of acute depression in bipolar I disorder. CNS Spectr. 2013;18(4):199-208.
26. Kadakia A, Dembek C, Heller V, *et al.* Efficacy and Tolerability of Atypical Antipsychotics for Acute Bipolar Depression: A Network Meta-Analysis. BMC Psychiatry. 2021 May 11;21(1):249.

27. Read JR, Sharpe L, Modini M, *et al.* Multimorbidity and Depression: A Systematic Review and Meta-Analysis. J Affect Disord. 2017 Oct;221:36-46.
28. Moussavi S, Chatterji S, Verdes E, *et al.* Depression, chronic diseases, and decrements in health: Results from the World Health Surveys. Lancet. 2007;370(9590):851-8.
29. Park M, Katon WJ, Wolf FM. Depression and Risk of Mortality in Individuals with Diabetes: A Meta-Analysis and Systematic Review. Gen Hosp Psychiatry. 2013;35(3):217-25.
30. Inoue K, Beekley J, Goto A, *et al.* Depression and Cardiovascular Disease Events among Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis with Bias Analysis. J Diabetes Complications. 2020 Dec;34(12):107710.
31. Lichtman JH, Bigger JT, Blumenthal JA, *et al.* Depression and Coronary Heart Disease: Recommendations for Screening, Referral, and Treatment: A Science Advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: Endorsed by the American Psychiatric Association. Circulation. 2008 Oct 21;118(17):1768-75.
32. Ormel J, Von Korff M, Burger H, *et al.* Mental disorders among persons with heart disease – results from World Mental Health surveys. Gen Hosp Psychiatry. 2007 Jul 1;29(4):325-34.
33. Baune BT, Stuart M, Gilmour A, *et al.* The Relationship Between Subtypes of Depression and Cardiovascular Disease: A Systematic Review of Biological Models. Transl Psychiatry. 2012 Mar 13;2:e92.
34. Schulman-Marcus J, Shah T, Swaminathan RV, *et al.* Comparison of recent trends in patients with and without major depression and acute ST-elevation myocardial infarction. Am J Cardiol. 2016 Sep 15;118(6):779-84.
35. Sani G, Tondo L, Undurraga J, *et al.* Melancholia: Does this ancient concept have contemporary utility? Int Rev Psychiatry Abingdon Engl. 2020 Sep;32(5-6):466-70.
36. Sneed JR, Reinlieb ME, Rutherford BR, *et al.* Antidepressant treatment of melancholia in older adults. Am J Geriatr Psychiatry. 2014;22(1):46-52.
37. Kolshus E, Jelovac A, McLoughlin DM. Bitemporal v. High-Dose Right Unilateral Electroconvulsive Therapy for Depression: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Psychol Med. 2017 Feb;47(3):518-30.
38. Brown WA. Treatment response in melancholia. Acta Psychiatr Scand Suppl. 2007(433):125-9.
39. von Wolff A, Hölzel LP, Westphal A, *et al.* Selective Serotonin Re-uptake Inhibitors and Tricyclic Antidepressants in the Acute Treatment of Chronic Depression and Dysthymia: A Systematic Review and Meta-Analysis. J Affect Disord. 2013 Jan;144(1-2):7-15.
40. Magni LR, Purgato M, Gastaldon C, *et al.* Fluoxetine versus other types of pharmacotherapy for depression. Cochrane Database Syst Rev. 2013(7):CD004185.
41. Leadholm AK, Rothschild AJ, Nolen WA, *et al.* The treatment of psychotic depression: Is there consensus among guidelines and psychiatrists? J Affect Disord. 2013;145(2):214-20.
42. Wijkstra J, Lijmer J, Burger H, *et al.* Pharmacological treatment for psychotic depression. Cochrane Database Syst Rev. 2013(11):CD004044.
43. American Psychiatric Association. Practice Guideline for the Treatment of Patients with Major Depressive Disorder. 3rd ed. Arlington VA: American Psychiatric Association (APA); 2010.
44. Kho KH, van Vreeswijk MF, Simpson S, *et al.* A Meta-Analysis of Electroconvulsive Therapy Efficacy in Depression. J ECT. 2003;19(3):139-47.
45. Group UER. Efficacy and Safety of Electro-Convulsive Therapy in Depressive Disorders: A Systematic Review and Meta-Analysis. Lancet. 2003;361 (9360):799-808.
46. Thase ME. The role of mono-amine oxidase inhibitors in depression treatment guidelines. J Clin Psychiatry. 2012;1:10-6.
47. Stewart JW, Thase ME. Treating DSM-IV depression with atypical features. J Clin Psychiatry. 2007;68(4):10.
48. Flockhart DA. Dietary restrictions and drug interactions with monoamine oxidase inhibitors: An update. J Clin Psychiatry. 2012 Jul;73 (suppl 1):17-24.
49. Penders TM, Stanciu CN, Schoemann AM, *et al.* Bright Light Therapy as Augmentation of Pharmacotherapy for Treatment of Depression: A Systematic Review and Meta-Analysis. Prim Care Companion CNS Disorders. 2016 Oct 20;18(5):26717.
50. Nussbaumer-Streit B, Thaler K, Chapman A, *et al.* Second-generation antidepressants for treatment of seasonal affective disorder. Cochrane Database Syst Rev. 2021(3):CD008591.
51. Kessler RC, Petukhova M, Sampson NA, *et al.* Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. Int J Methods Psychiatr Res. 2012;21(3):169 84.
52. Kessler RC, Sampson NA, Berglund P, *et al.* Anxious and non-anxious major depressive disorder in the World. Health Organ World Ment Health Surv Epidemiol Psychiatr Sci. 2015;1-17.
53. Ogawa Y, Takeshima N, Hayasaka Y, *et al.* Antidepressants plus benzodiazepines for adults with major depression. Cochrane Database Syst Rev. 2019(6):CD001026.
54. Andersen AM, Pietrzak RH, Kranzler HR, *et al.* Polygenic scores for major depressive disorder and risk of alcohol dependence. JAMA Psychiatry. 2017 Nov 1;74(11):1153.

55. Lingford-Hughes AR, Welch S, Peters L, *et al.* BAP updated guidelines: Evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and comorbidity: Recommendations from BAP. J Psychopharmacol Oxf Engl. 2012 Jul;26(7):899-952.
56. Taylor DM, Barnes TR, Young AH. The Maudsley Prescribing Guidelines in Psychiatry. 14th edition. Chichester, West Sussex. Hoboken, NJ.: John Wiley & Sons; 2021.
57. Norris DR, Clark MS. The suicidal patient: Evaluation and management. Am Fam Physician. 2021 Apr 1;103(7):417-21.
58. Brent DA. Antidepressants and Suicidality. Psychiatr Clin North Am. 2016 Sep;39(3):503-12.
59. McDonagh MS, Matthews A, Phillipi C, *et al.* Depression Drug Treatment Outcomes in Pregnancy and the Postpartum Period: A Systematic Review and Meta-Analysis. Obstet Gynecol. 2014 Sep;124(3):526-34.
60. Zhang T-N, Gao S-Y, Shen Z-Q, *et al.* Use of Selective Serotonin Re-Uptake Inhibitors in the First Trimester and Risk of Cardiovascular-Related Malformations: A Meta-Analysis of Cohort Studies. Sci Rep. 2017 Mar;7(1):43085.
61. Grigoriadis S, Vonderporten EH, Mamisashvili L, *et al.* Prenatal Exposure to Antidepressants and Persistent Pulmonary Hypertension of the Newborn: Systematic Review and Meta-Analysis. BMJ. 2014;348:6932.
62. Yonkers KA, Blackwell KA, Glover J, *et al.* Antidepressant use in pregnant and postpartum women. Annu Rev Clin Psychol. 2014 Mar 28;10(1):369-92.
63. Becker M, Weinberger T, Chandy A, *et al.* Depression during pregnancy and postpartum. Curr Psychiatry Rep. 2016 Mar;18(3):32.
64. Yonkers KA, Wisner KL, Stewart DE, *et al.* The management of depression during pregnancy: A report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. Gen Hosp Psychiatry. 2009;31(5):403-13.
65. Kim DR, Epperson CN, Weiss AR, *et al.* Pharmacotherapy of postpartum depression: An update. Expert Opin Pharmacother. 2014; 15(9):1223-34.
66. Sockol LE, Epperson CN, Barber JP. Preventing Postpartum Depression: A Meta-Analytic Review. Clin Psychol Rev. 2013;33(8):1205-17.
67. Zheng W, Cai D-B, Zheng W, *et al.* Brexanolone for Postpartum Depression: A Meta-Analysis of Randomized Controlled Studies. Psychiatry Res. 2019 Sep;279:83-9.
68. Bellantuono C, Vargas M, Mandarelli G, *et al.* The safety of serotonin-noradrenaline re-uptake inhibitors (SNRIs) in pregnancy and breastfeeding: A comprehensive review: SNRIs in pregnancy and breastfeeding. Hum Psychopharmacol Clin Exp. 2015 May;30(3):143-51.
69. Fischer Fumeaux CJ, Morisod Harari M, Weisskopf E, *et al.* Risk-benefit balance assessment of SSRI antidepressant use during pregnancy and lactation based on best available evidence – an update. Expert Opin Drug Saf. 2019 Oct;18(10):949-63.
70. Berle JO, Spigset O. Antidepressant use during breastfeeding. Curr Womens Health Rev. 2011;7(1):28-34.
71. Toffol E, Heikinheimo O, Partonen T. Hormone therapy and mood in perimenopausal and postmenopausal women: A narrative review. Menopause. 2015 May;22(5):564-78.
72. Musial N, Ali Z, Grbevski J, *et al.* Peri-menopause and first-onset mood disorders: A closer look. FOCUS. 2021 Jul;19(3):330-7.
73. Spina E, de Leon J. Clinically relevant interactions between newer antidepressants and second-generation antipsychotics. Expert Opin Drug Metab Toxicol. 2014 May;10(5):721-46.
74. Spina E, Santoro V, D'Arrigo C. Clinically relevant pharmacokinetic drug interactions with second-generation antidepressants: An update. Clin Ther. 2008;30(7):1206-27.
75. Castaldelli-Maia JM, Hofmann C, Chagas ACP, *et al.* Major Cardiac-Psychiatric Drug-Drug Interactions: A Systematic Review of the Consistency of Drug Databases. Cardiovasc Drugs Ther. 2021;35(3):441-54.
76. Roose SP, Glassman AH, Giardina EG, *et al.* Tricyclic antidepressants in depressed patients with cardiac conduction disease. Arch Gen Psychiatry. 1987;44(3):273-5.
77. Mavrides N, Nemeroff C. Treatment of depression in cardiovascular disease. Depress Anxiety. 2013;30(4):328-41.
78. Hasnain M, Howland RH, Vieweg WVR. Escitalopram and QTc prolongation. J Psychiatry Neurosci. 2013;38(4):11.
79. Beach SR, Kostis WJ, Celano CM, *et al.* Meta-Analysis of Selective Serotonin Re-Uptake Inhibitor-Associated QTc Prolongation. J Clin Psychiatry. 2014 May;75(5):e441-449.
80. Villa RF, Ferrari F, Moretti A. Post-stroke depression: Mechanisms and pharmacological treatment. Pharmacol Ther. 2018 Apr;184:131-44.
81. Feng C, Fang M, Liu X-Y. The neurobiological pathogenesis of poststroke depression. Sci World J. 2014;2014:1-8.
82. Carson AJ, MacHale S, Allen K, *et al.* Depression after stroke and lesion location: A systematic review. Lancet. 2000;356(9224):122-6.
83. Mortensen JK, Andersen G. Pharmacological management of post-stroke depression: An update of the evidence and clinical guidance. Expert Opin Pharmacother. 2021;22(9):1157-66.
84. Allida S, Cox KL, Hsieh C-F, *et al.* Pharmacological, psychological, and non-invasive brain stimulation interventions for treating depression

after stroke. Cochrane Database Syst Rev. 2020(1):CD003437.
85. Kanner AM. Most antidepressant drugs are safe for patients with epilepsy at therapeutic doses: A review of the evidence. Epilepsy Behav. 2016 Aug;61:282-6.
86. Maguire MJ, Marson AG, Nevitt SJ. Antidepressants for people with epilepsy and depression. Cochrane Database Syst Rev. 2021(4):CD010682.
87. Green AR, Reifler LM, Boyd CM, *et al.* Medication profiles of patients with cognitive impairment and high anticholinergic burden. Drugs Aging. 2018 Mar;35(3):223-32.
88. Gautam S, Jain A, Gautam M, *et al.* Clinical practice guidelines for the management of depression. Indian J Psychiatry. 2017;59(5):34.
89. Gabriel FC, de Melo DO, Fráguas R, *et al.* Pharmacological Treatment of Depression: A Systematic Review Comparing Clinical Practice Guideline Recommendations. PloS One. 2020;15(4):e0231700.
90. Cipriani A, Furukawa TA, Salanti G, *et al.* Comparative Efficacy and Acceptability of 21 Antidepressant Drugs for the Acute Treatment of Adults with Major Depressive Disorder: A Systematic Review and Network Meta-Analysis. The Lancet. 2018 Apr;391(10128):1357-66.
91. Huang K-L, Lu W-C, Wang Y-Y, *et al.* Comparison of Agomelatine and Selective Serotonin Re-uptake Inhibitors/Serotonin-Norepinephrine Re-uptake Inhibitors in Major Depressive Disorder: A Meta-Analysis of Head-to-Head Randomized Clinical Trials. Aust N Z J Psychiatry. 2014 Jul;48(7):663-71.
92. Chekroud AM, Gueorguieva R, Krumholz HM, *et al.* Reevaluating the efficacy and predictability of antidepressant treatments: A symptom clustering approach. JAMA Psychiatry. 2017 Apr 1;74(4):370.
93. Witkin JM, Martin AE, Golani LK, *et al.* Rapid-acting antidepressants. Advances in Pharmacology. 2019 Jan 1;86:47-96.
94. Boyce P, Ma C. Choosing an antidepressant. Aust Prescr. 2021 Feb;44(1):12-5.
95. Cleare A, Pariante CM, Young AH, *et al.* Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. J Psychopharmacol. 2015 May; 29(5):459-525.
96. Bauer M, Pfennig A, Severus E, *et al.* World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders, part 1: Update 2013 on the acute and continuation treatment of unipolar depressive disorders. World J Biol Psychiatry. 2013 Jul;14(5):334-85.
97. Solmi M, Miola A, Croatto G, *et al.* How can we improve antidepressant adherence in the management of depression? A targeted review and 10 clinical recommendations. Braz J Psychiatry. 2021 Apr;43(2):189-202.
98. Wang S-M, Han C, Bahk W-M, *et al.* Addressing the Side Effects of Contemporary Antidepressant Drugs: A Comprehensive Review. Chonnam Med J. 2018;54(2):101-12.
99. Luxton R, Kyriakopoulos M. Depression in children and young people: Identification and management NICE guidelines. Arch Dis in Child Educ Pract. 2022 Feb 1;107(1):36-8.
100. Kok RM, Reynolds CF. Management of Depression in Older Adults: A Review. JAMA. 2017 May 23;317(20):2114.
101. Fagiolini A, Albert U, Ferrando L, *et al.* A randomized, double-blind study comparing the efficacy and safety of trazodone once-a-day and venlafaxine extended-release for the treatment of patients with major depressive disorder. Int Clin Psychopharmacol. 2020 May; 35(3):137-46.
102. Furukawa TA, Cipriani A, Cowen PJ, *et al.* Optimal Dose of Selective Serotonin Re-Uptake Inhibitors, Venlafaxine, and Mirtazapine in Major Depression: A Systematic Review and Dose-Response Meta-Analysis. Lancet Psychiatry. 2019 Jul;6(7):601-9.
103. Hartmann-Boyce J, Stead LF, Cahill K, *et al.* Efficacy of interventions to combat tobacco addiction: Cochrane update of 2013 reviews. Addiction. 2014;109(9):1414-25.
104. Hughes JR, Stead LF, Hartmann-Boyce J, *et al.* Antidepressants for smoking cessation. Cochrane Database Syst Rev. 2014(1):CD000031.
105. Reichenpfader U, Gartlehner G, Morgan LC, *et al.* Sexual dysfunction associated with second-generation antidepressants in patients with major depressive disorder: Results from a systematic review with network Meta-Analysis. Drug Saf. 2014;37:19-31.
106. Taylor D, Sparshatt A, Varma S, *et al.* Antidepressant Efficacy of Agomelatine: Meta-Analysis of Published and Unpublished Studies. BMJ. 2014;348:1888.
107. Baldwin DS, Hanumanthaiah VB. Vortioxetine in the treatment of major depressive disorder. Future Neurol. 2015 Mar;10(2):79-89.
108. Llorca PM, Lancon C, Brignone M, *et al.* Relative efficacy and tolerability of vortioxetine versus selected antidepressants by indirect comparisons of similar clinical studies. Curr Med Res Opin. 2014;30(12):2589-606.
109. Prasitlumkum N, Cheungpasitporn W, Tokavanich N, *et al.* Antidepressants and Risk of Sudden Cardiac Death: A Network Meta-Analysis and Systematic Review. Med Sci. 2021 Apr 23;9(2):26.
110. Nelson JC. Tricyclic and tetracyclic drugs. In: The American Psychiatric Association Publishing Textbook of Psychopharmacology. 5th ed. Arlington, VA: American Psychiatric Association Publishing; 2017 May 10:305-34.

111. Mottram P, Wilson K, Strobl J. Antidepressants for depressed elderly. Cochrane Database Syst Rev. 2006(1):CD003491.
112. Apaydin EA, Maher AR, Shanman R, *et al.* A systematic review of St. John's wort for major depressive disorder. Syst Rev. 2016 Sep 2;5(1):148.
113. Nicolussi S, Drewe J, Butterweck V, *et al.* Clinical relevance of St. John's wort drug interactions revisited. Br J Pharmacol. 2020 Mar;177(6):1212-26.
114. Gartlehner G, Wagner G, Matyas N, *et al.* Pharmacological and Non-Pharmacological Treatments for Major Depressive Disorder: Review of Systematic Reviews. BMJ Open. 2017 Jun 14;7(6):e014912.
115. Li G, Mbuagbaw L, Samaan Z, *et al.* Efficacy of Vitamin D Supplementation in Depression in Adults: A Systematic Review. J Clin Endocrinol Metab. 2014;99(3):757-67.
116. Ravindran AV, Balneaves LG, Faulkner G, *et al.* Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 5. Complementary and Alternative Medicine Treatments. Can J Psychiatry. 2016 Sep;61(9):576-87.
117. Dos Santos RG, Bouso JC, Alcázar-Córcoles MÁ, *et al.* Efficacy, Tolerability, and Safety of Serotonergic Psychedelics for the Management of Mood, Anxiety, and Substance-Use Disorders: A Systematic Review of Systematic Reviews. Expert Rev Clin Pharmacol. 2018 Sep;11(9): 889-902.
118. Goldberg SB, Shechet B, Nicholas CR, *et al.* Post-Acute Psychological Effects of Classical Serotonergic Psychedelics: A Systematic Review and Meta-Analysis. Psychol Med. 2020 Dec;50(16):2655-66.
119. Li NX, Hu YR, Chen WN, *et al.* Dose Effect of Psilocybin on Primary and Secondary Depression: A Preliminary Systematic Review and Meta-Analysis. J Affect Disord. 2022 Jan 1;296:26-34.
120. Psiuk D, Nowak E, Cholewa K, *et al.* The Potential Role of Serotonergic Hallucinogens in Depression Treatment. Life Basel. 2021 Jul 29;11(8).
121. Stanciu CN, Brunette MF, Teja N, *et al.* Evidence for Use of Cannabinoids in Mood Disorders, Anxiety Disorders, and PTSD: A Systematic Review. Psychiatr Serv. 2021 Apr 1;72(4):429-36.
122. Hindley G, Beck K, Borgan F, *et al.* Psychiatric Symptoms Caused by Cannabis Constituents: A Systematic Review and Meta-Analysis. Lancet Psychiatry. 2020 Apr;7(4):344-53.
123. Fabbri C, Minarini A, Niitsu T, *et al.* Understanding the pharmacogenetics of selective serotonin re-uptake inhibitors. Expert Opin Drug Metab Toxicol. 2014;10(8):1093-118.
124. Fabbri C, Porcelli S, Serretti A. From pharmacogenetics to pharmacogenomics: The way toward the personalization of antidepressant treatment. Can J Psychiatry. 2014;59(2):62-75.
125. Alemi F, Min H, Yousefi M, *et al.* Effectiveness of common antidepressants: A post market release study. EClinicalMedicine. 2021 Nov;41:101171.
126. Fond G, Loundou A, Rabu C, *et al.* Ketamine Administration in Depressive Disorders: A Systematic Review and Meta-Analysis. Psychopharmacol Berl. 2014;231(18):3663-76.
127. Zhu M, Hong RH, Yang T, *et al.* The Efficacy of Measurement-Based Care for Depressive Disorders: Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Clin Psychiatry. 2021 Sep 28;82(5):21r14034.
128. Wagner G, Schultes M-T, Titscher V, *et al.* Efficacy and Safety of Levomilnacipran, Vilazodone and Vortioxetine Compared with Other Second-Generation Antidepressants for Major Depressive Disorder in Adults: A Systematic Review and Network Meta-Analysis. J Affect Disord. 2018 Mar;228:1-12.
129. Cheng Q, Huang J, Xu L, *et al.* Analysis of time-course, dose-effect, and influencing factors of antidepressants in the treatment of acute adult patients with major depression. Int J Neuropsychopharmacol. 2020 Mar 25;23(2):76–87.
130. Ramanuj P, Ferenchick EK, Pincus HA. Depression in primary care: Part 2 – management. BMJ. 2019 Apr 8;l835.
131. Kraus C, Kadriu B, Lanzenberger R, *et al.* Prognosis and improved outcomes in major depression: A review. Transl Psychiatry. 2019 Dec;9(1):127.
132. Kaymaz N, van Os J, Loonen AJ, *et al.* Evidence that Patients with Single Versus Recurrent Depressive Episodes are Differentially Sensitive to Treatment Discontinuation: A Meta-Analysis of Placebo-Controlled Randomized Trials. J Clin Psychiatry. 2008;69(9):1423-36.
133. Tokuoka H, Takahashi H, Ozeki A, *et al.* Trajectories of depression symptom improvement and associated predictor analysis: An analysis of duloxetine in double-blind placebo-controlled trials. J Affect Disord. 2016 May;196:171-80.
134. Watanabe N, Maruo K, Imai H, *et al.* Predicting Antidepressant Response Through Early Improvement of Individual Symptoms of Depression Incorporating Baseline Characteristics of Patients: An Individual Patient Data Meta-Analysis. J Psychiatr Res. 2020 Jun;125:85-90.
135. Cox GR, Callahan P, Churchill R, *et al.* Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents. Cochrane Database Syst Rev. 2014(11):CD008324.
136. Machmutow K, Meister R, Jansen A, *et al.* Comparative effectiveness of continuation and maintenance treatments for persistent depressive disorder in adults. Cochrane Database Syst Rev. 2019(5):CD012855.

137. Breedvelt JJF, Brouwer ME, Harrer M, *et al.* Psychological Interventions as an Alternative and Add-on to Antidepressant Medication to Prevent Depressive Relapse: Systematic Review and Meta-Analysis. Br J Psychiatry J Ment Sci. 2021 Oct;219(4):538-45.
138. Carvalho AF, Berk M, Hyphantis TN, *et al.* The integrative management of treatment-resistant depression: A comprehensive review and perspectives. Psychother Psychosom. 2014;83(2):70-88.
139. MacQueen G, Santaguida P, Keshavarz H, *et al.* Systematic Review of Clinical Practice Guidelines for Failed Antidepressant Treatment Response in Major Depressive Disorder, Dysthymia, and Subthreshold Depression in Adults. Can J Psychiatry. 2017 Jan;62(1):11-23.
140. Rhee TG, Rosenheck RA. Psychotropic polypharmacy reconsidered: Between-class polypharmacy in the context of multimorbidity in the treatment of depressive disorders. J Affect Disord. 2019 Jun;252:450-7.
141. Undurraga J, Sim K, Tondo L, *et al.* Lithium Treatment for Unipolar Major Depressive Disorder: Systematic Review. J Psychopharmacol. 2019 Feb;33(2):167-76.
142. Nelson JC, Baumann P, Delucchi K, *et al.* A Systematic Review and Meta-Analysis of Lithium Augmentation of Tricyclic and Second Generation Antidepressants in Major Depression. J Affect Disord. 2014;168:269-75.
143. Smith KA, Cipriani A. Lithium and suicide in mood disorders: Updated meta-review of the scientific literature. Bipolar Disord. 2017 Nov;19(7):575-86.
144. Lin CY, Tsai GE, Wang HS, *et al.* Effectiveness of aripiprazole, olanzapine, quetiapine, and risperidone augmentation treatment for major depressive disorder: A nationwide population-based study. J Clin Psychiatry. 2014;75(9):924-31.
145. Vázquez GH, Bahji A, Undurraga J, *et al.* Efficacy and tolerability of combination treatments for major depression: Antidepressants plus second-generation antipsychotics vs. esketamine vs. lithium. J Psychopharmacol (Oxf). 2021 Aug;35(8):890-900.
146. Davies P, Ijaz S, Williams CJ, *et al.* Pharmacological interventions for treatment-resistant depression in adults. Cochrane Database Syst Rev. 2019(12):CD010557.
147. Rafeyan R, Papakostas GI, Jackson WC, *et al.* Inadequate response to treatment in major depressive disorder: Augmentation and adjunctive strategies. J Clin Psychiatry. 2020 May 12;81(3):27570.
148. Voineskos D, Daskalakis ZJ, Blumberger DM. Management of treatment-resistant depression: Challenges and strategies. Neuropsychiatr Dis Treat. 2020 Jan;Volume 16:221-34.
149. Zhao S, Xia Y, Huang Y, *et al.* The correlation between thyroid function, frontal gray matter, and executive function in patients with major depressive disorder. Front Endocrinol. 2021 Nov 23;12:779693.
150. Zhou X, Ravindran AV, Qin B, *et al.* Comparative Efficacy, Acceptability, and Tolerability of Augmentation Agents in Treatment-Resistant Depression: Systematic Review and Network Meta-Analysis. J Clin Psychiatry. 2015 Apr 22;76(04):e487-98.
151. Kishi T, Miyake N, Okuya M, *et al.* N-Acetylcysteine as an Adjunctive Treatment for Bipolar Depression and Major Depressive Disorder: A Systematic Review and Meta-Analysis of Double-Blind, Randomized Placebo-Controlled Trials. Psychopharmacology (Berl). 2020 Nov;237(11):3481-7.
152. Henssler J, Bschor T, Baethge C. Combining Antidepressants in Acute Treatment of Depression: A Meta-Analysis of 38 Studies Including 4511 Patients. Can J Psychiatry. 2016 Jan;61(1):29-43.
153. Kessler D, Burns A, Tallon D, *et al.* Combining mirtazapine with SSRIs or SNRIs for treatment-resistant depression: The MIR RCT. Health Technol Assess Winch Engl. 2018 Nov;22(63):1-136.
154. Bennabi D, Aouizerate B, El-Hage W, *et al.* Risk Factors for Treatment Resistance in Unipolar Depression: A Systematic Review. J Affect Disord. 2015;171:137-41.
155. Newton-Howes G, Tyrer P, Johnson T, *et al.* Influence of Personality on the Outcome of Treatment in Depression: Systematic Review and Meta-Analysis. J Disord. 2014;28(4):577-93.
156. Kudlow PA, McIntyre RS, Lam RW. Early switching strategies in antidepressant non-responders: Current evidence and future research directions. CNS Drugs. 2014;28(7):601-9.
157. Brignone M, Diamand F, Painchault C, *et al.* Efficacy and tolerability of switching therapy to vortioxetine versus other antidepressants in patients with major depressive disorder. Curr Med Res Opin. 2016 Feb;32(2):351-66.
158. Boyce P, Hopwood M, Morris G, *et al.* Switching antidepressants in the treatment of major depression: When, how and what to switch to? J Affect Disord. 2020 Jan;261:160-3.
159. Muscatello MR, Bruno A, De Fazio P, *et al.* Augmentation strategies in partial responder and/or treatment-resistant schizophrenia patients treated with clozapine. Expert Opin Pharmacother. 2014;15(16):2329-45.
160. Swainson J, McGirr A, Blier P, *et al.* The Canadian Network for Mood and Anxiety Treatments (CANMAT) Task Force Recommendations for the Use of Racemic Ketamine in Adults with Major Depressive Disorder: Recommandations du Groupe de Travail du Réseau Canadien

pour les Traitements de l'Humeur et de l'Anxiété (Canmat) Concernant l'Utilisation de la Kétamine Racémique chez les Adultes Souffrant de Trouble Dépressif Majeur. Can J Psychiatry. 2021 Feb;66(2):113-25.
161. Ren J, Li H, Palaniyappan L, *et al.* Repetitive Transcranial Magnetic Stimulation Versus Electroconvulsive Therapy for Major Depression: A Systematic Review and Meta-Analysis. Prog Neuropsychopharmacol Biol Psychiatry. 2014;51:181-9.
162. Cook IA, Espinoza R, Leuchter AF. Neuromodulation for depression: Invasive and noninvasive (deep brain stimulation, transcranial magnetic stimulation, trigeminal nerve stimulation). Neurosurg Clin N Am. 2014;25(1):103-16.
163. Shiozawa P, Fregni F, Bensenor IM, *et al.* Transcranial Direct Current Stimulation for Major Depression: An Updated Systematic Review and Meta-Analysis. Int J Neuropsychopharmacol. 2014;17(9):1443-52.
164. Lobo RA, Davis SR, de Villiers TJ, *et al.* Prevention of diseases after menopause. Climacteric. Vol. 17. 2014. p. 540-56.
165. Mehta D, Newport DJ, Frishman G, *et al.* Early predictive biomarkers for postpartum depression point to a role for estrogen receptor signaling. Psychol Med. 2014;1-14.
166. Ijaz S, Davies P, Williams CJ, *et al.* Psychological therapies for treatment-resistant depression in adults. Cochrane Database Syst Rev. 2018(5):CD010558.
167. van Bronswijk S, Moopen N, Beijers L, *et al.* Effectiveness of Psychotherapy for Treatment-Resistant Depression: A Meta-Analysis and Meta-regression. Psychol Med. 2019 Feb;49(3):366-79.

6: Panic Disorder and Social Anxiety Disorder

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Two of the anxiety disorders – panic disorder and social anxiety disorder (social phobia) – are among the most common of the psychiatric disorders.[1,2] Each may be characterised by panic attacks or hyperarousal, and panic disorder especially may be misdiagnosed as a physical illness in primary care settings.[3] In addition, each may be associated with significant morbidity and functional impairment – it has been demonstrated that the anxiety disorders significantly contribute to the costs of all mental illness.[4-6] The role of psychotherapy in the treatment of panic disorder and social anxiety disorder must be emphasised.[7-10] Cognitive-behavioural psychotherapy can augment the anxiolytic effects of medication, is essential in reducing avoidance behaviours (e.g., agoraphobia, avoidance of social situations), and may be important in ultimately allowing medication discontinuation.[7,11-13] In addition, CBT has been shown to be effective when delivered digitally as well as face to face[14], and psycho-education of both patient and family is crucial in the treatment of anxiety disorders.[15,16]

This algorithm assumes that the patient is an adult. Although there are fewer data on the treatment of children and adolescents with these disorders, what does exist suggests that a similar approach may be useful in some younger patients.[17,18] Specialist consultation may, however, be indicated in such cases, and cognisance should be taken of the possible increased risk of suicidal behaviour in adolescents using SSRIs.

STEP 1: DIAGNOSIS OF PANIC DISORDER, SOCIAL ANXIETY DISORDER

The first step in any treatment algorithm involves correct diagnosis. Panic attacks (see Table 6.1.) may be present in panic disorder and social anxiety disorder, although shortness of breath may be more common in the

Table 6.1. Diagnostic guidelines for panic attack (adapted from ICD-11)

A discrete episode of intense fear or apprehension, in which a number of the following symptoms develop rapidly and concurrently, and usually reach a peak within 10 minutes:
1. Palpitations, pounding heart, or increased heart rate
2. Sweating
3. Trembling or shaking
4. Sensations of shortness of breath or smothering
5. Feeling of choking
6. Chest pain or discomfort
7. Nausea or abdominal distress
8. Feeling dizzy, unsteady, lightheaded, or faint
9. Chills or hot flushes
10. Paraesthesias (numbness or tingling sensations)
11. Derealisation (feelings of unreality) or depersonalisation (being detached from oneself)
12. Fear of losing control or "going crazy"
13. Fear of imminent death
Panic attacks may be triggered by particular situations, or may appear out of the blue

panic attacks of panic disorder; blushing and stuttering may be more common in those of social anxiety disorder. Panic attacks in panic disorder (see Table 6.2.) may be spontaneous or caused by exposure to stimuli previously associated with a panic attack (e.g., a confined space), while panic attacks in social anxiety disorder (see Table 6.3.) are cued by feared social situations (e.g., public speaking).[19]

The initial evaluation should include assessment of the severity and frequency of panic attacks and hyperarousal, the degree of avoidance behaviour, and the extent of functional impairment. Panic disorder and social anxiety disorder may both be associated with other psychiatric symptoms, particularly depressive and substance-abuse symptoms, which therefore also deserve particular attention.[20,21]

Panic attacks may occur in other psychiatric disorders, such as depression, specific phobias, obsessive-compulsive and related disorders, post-traumatic stress disorder and substance-use disorders. In addition, certain general medical conditions (e.g., hyperthyroidism) may present with panic attacks.[22] Caffeine may induce or exacerbate panic attacks as well.[23] A thorough medical history, physical examination, and routine blood as well as urine tests, are therefore useful in patients presenting with panic attacks.

Table 6.2. Diagnostic guidelines for panic disorder (adapted from ICD-11)

1. Recurrent panic attacks (Table 6.1.), some of which are unexpected, or "out of the blue"
2. At least one of the attacks has been followed by persistent concern about having additional attacks, or their negative significance, or behaviours intended to avoid their recurrence.
3. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism, cardiopulmonary disorders).
4. The disturbance is not better explained by another mental disorder.
5. The symptoms result in significant impairment in personal, family, social, educational, occupational, or other important areas of functioning. If functioning is maintained, it is only through significant additional effort.

Table 6.3. Diagnostic guidelines for social anxiety disorder (adapted from ICD-11)

1 A marked and excessive fear or anxiety that occurs in one or more social situations, such as social interactions (e.g., having a conversation), doing something while feeling observed (e.g., eating or drinking around others), or performing in front of others (e.g., giving a speech).
2 The individual fears acting in a way (or showing anxiety symptoms) that will be humiliating or embarrassing (negatively evaluated by others).
3 The social situations almost always provoke fear or anxiety.
4 The social situations are avoided or endured with intense fear or anxiety.
5 The fear or anxiety is out of proportion to the actual threat posed by the social situation and to the sociocultural context.
6 The symptoms are persistent, typically lasting for an extended period (several months)
7 The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.
8 The symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.
9 The symptoms are not better explained by another mental disorder (e.g., agoraphobia, body dysmorphic disorder, olfactory reference disorder).
Specify if: Performance only: if the fear is restricted to speaking or performing in public.

STEP 2: COMPLICATIONS IN DIAGNOSIS IMPACTING PHARMACOTHERAPY

Panic disorder and social anxiety disorder may be complicated in several ways, impacting on decisions about pharmacotherapy. Brief explanations of these complicating factors and their implications for pharmacotherapy follow:

a. **Severity:** Patients with severe symptoms may require brief hospitalisation to help contain symptoms. The possible association between anxiety disorders and increased risk of suicide[24], for example, needs to be taken seriously. In addition, acute administration of high-potency benzodiazepines (e.g., alprazolam, clonazepam) may be necessary. Slow-release preparations or benzodiazepines with longer half-lives (e.g., clonazepam) have the advantage of avoiding rebound anxiety between doses. While high-potency benzodiazepines have been shown to be effective in panic disorder and in social anxiety disorder in controlled trials[25,26], we recommend that these agents, in view of their dependence potential, be reserved for acute rapid anxiety reduction in patients with severe symptoms and not routinely used for long-term management.[27,28]

b. **Melancholia:** Melancholic features of depression include loss of pleasure in activities, lack of reactivity to pleasurable stimuli, and various neurovegetative symptoms, such as exacerbation of depression in the morning, early-morning awakening, and significant weight loss.[29] Patients with melancholia appear to respond better to antidepressants and electroconvulsive therapy and less favourably to psychotherapy and placebo than do non-melancholic patients.[30,31] In addition, there is some evidence that older drugs, such as tricyclic antidepressants (TCAs), may be more effective than selective serotonin re-uptake inhibitors (SSRIs) in patients with depression accompanied by melancholic features and hospitalised inpatients[30,32], although not all evidence is consistent.[30]

c. **Alcohol and/or substance use:** Alcohol and other substance-use disorders are associated with exacerbation of anxiety disorders. On the other hand, anxiety disorders may lead to the use of alcohol and other substances in order to self-medicate anxiety. Thus, although it is generally advisable to detoxify patients prior to beginning pharmacotherapy, in some cases such pharmacotherapy is an integral part of the treatment of the secondary substance-use disorder.[20,33] There is some evidence that the SSRIs, in particular, may be useful for the treatment of anxiety disorders with a comorbid alcohol-use disorder, whereas benzodiazepines are relatively contra-indicated in these patients.[33]

d. **Pregnancy, lactation, menopause:** Pharmacotherapy should ideally be avoided during pregnancy and lactation. Nevertheless, where clinical considerations outweigh the risk of medication, such intervention should be considered after consultation with a specialist. Adverse-pregnancy-outcome studies can be difficult to interpret and it is not always clear whether outcomes observed are due to medications themselves or confounders such as the underlying mental illness.[34] SSRIs are generally considered safe first-line agents in pregnancy and there is currently no conclusive evidence of an association between treatment with these agents and increased risk for malformations, preterm birth, low birth weight or small-for-gestational-age births.[34] However, fluoxetine and paroxetine use in early pregnancy may be associated with a small increased risk for cardiovascular malformations and initiation of these agents should be avoided in the first trimester.[34] The risk of persistent pulmonary hypertension of the newborn has been shown to be increased for infants exposed to SSRIs in late pregnancy, although clinically the absolute risk is low.[35] Benzodiazepine use during pregnancy is not contra-indicated, but has been associated with an increased risk of cleft palate, preterm delivery and low birth weight.[36,37] If used, the lowest effective dose of the benzodiazepine should be prescribed for the shortest possible duration, and high peak concentrations should be avoided by dividing the daily dosage into two or three doses.

e. **Comorbid medical disorders and medications:** Clinicians need to be aware of the multiple interactions between medications used in the treatment of the anxiety disorders and other medications, as well as of the impact of medication

adverse effects on medical disorders.[22] Fortunately, certain SSRIs have relatively few interactions with other medications, and the SSRIs as a class are well tolerated in most medical disorders.

STEP 3: FIRST-LINE PHARMACOTHERAPY

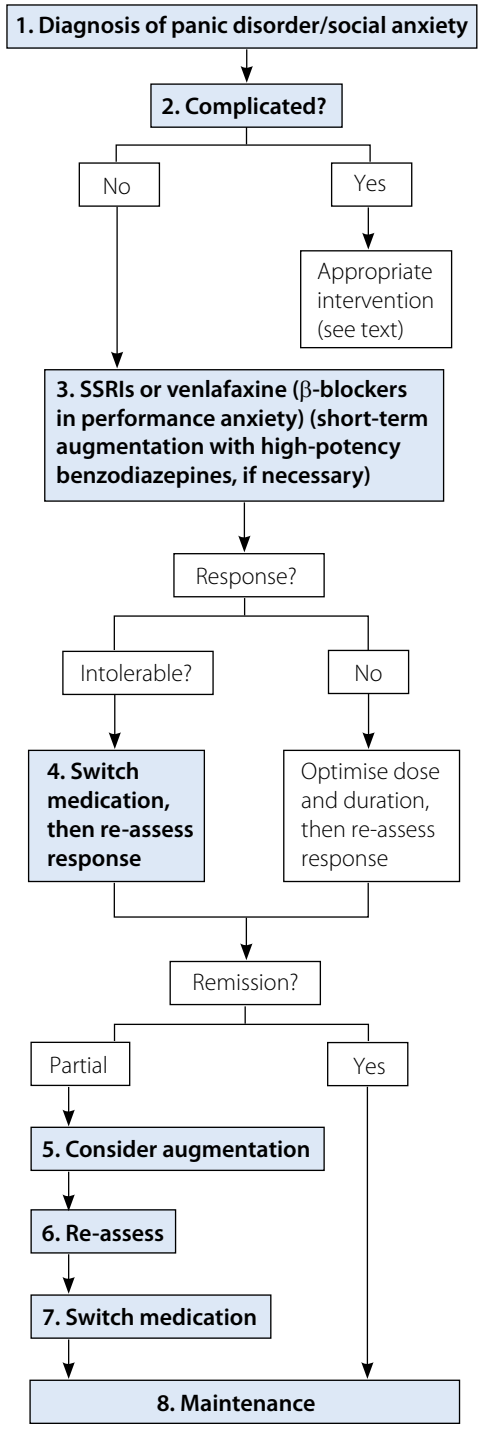
In the algorithm (see Figure 6.1.), SSRIs or venlafaxine are suggested to be the first-line treatment of panic disorder and social anxiety disorder. There is now a great deal of evidence that SSRIs are both well tolerated and effective in these disorders.[11,25,26,38-41] More recently, venlafaxine has been shown useful in panic disorder and in social anxiety disorder.[5]

Panic disorder also responds to certain other antidepressants, including imipramine, clomipramine, mirtazapine and phenelzine.[25,42] The relatively poor tolerability and safety profile of the tricyclics and other older antidepressants, such as the mono-amine oxidase inhibitors, mean that these agents should be avoided as first-line medications.[43] Irrespective of which antidepressant is used in the treatment of panic disorder, it is crucial to initiate treatment with very low doses (e.g., fluoxetine 5 mg) in order to prevent early exacerbation of panic attacks.[44]

Social anxiety disorder does not respond to the tricyclic antidepressants (with the possible exception of clomipramine, a predominantly serotonergic tricyclic). These agents should therefore not be used as first-line treatments of this disorder. When social anxiety symptoms are limited only to specific performance situations ('performance anxiety'), beta blockers can be prescribed on an as-needed basis.[45] These agents appear particularly useful for reducing 'peripheral' symptoms of anxiety, such as tremor and palpitations.[46] However, there are growing data that the SSRIs are useful not only in more generalised social anxiety disorder (when symptoms extend to most social situations), but also in social anxiety present in only one or two settings.[46]

When it comes to choosing a particular first-line treatment in panic disorder, it is worth bearing in mind that in panic disorder there appears to be little difference between individual SSRIs and between SSRIs and venlafaxine, whereas in social anxiety disorder, the current data suggest there may be greater efficacy for some SSRIs, such as paroxetine.[17,41,42,46] Of course, agents that have

Figure 6.1. Algorithm for pharmacotherapy of panic disorder and social anxiety disorder



proved efficacious and tolerable in a particular individual in the past should be favoured in the present, and vice versa. Similarly, despite an absence of supporting empirical data, many clinicians suggest that family history of response to a particular antidepressant favours the choice of that agent.

Important aspects of psycho-education regarding the SSRIs and SNRIs include the fact that these are not addictive, that despite being termed "antidepressants" they are highly efficacious in anxiety disorders, that side effects are typically transient, that therapeutic response is relatively slow in onset, and that if one agent does not work another should be tried.[44]

High-potency benzodiazepines (alprazolam, clonazepam) have also been shown to be efficacious in the treatment of panic disorder and social anxiety disorder.[27,43] Some authors have suggested that high-potency benzodiazepines qualify as first-line monotherapies in panic disorder and social anxiety disorder[47], but other authors have emphasised the potential problems of long-term treatment.[48] A compromise is that short-term augmentation of antidepressant agents with benzodiazepines may be useful in rapidly stabilising symptoms, and should therefore be considered when high levels of anxiety threaten to disrupt ongoing pharmacotherapy.[5,43]

Although ß-blockers are often prescribed by primary care practitioners for anxiety symptoms, there is not sufficient evidence to include them as a first-line medication for panic disorder or social anxiety disorder. Similarly, given their disadvantageous side-effect profiles (including tardive dyskinesia), we would be cautious about the use of low-dose antipsychotic medications in the first-line treatment of anxiety symptoms.[49]

STEP 4: ASSESS RESPONSE TO TREATMENT

To determine response to medication, it is important to ask about change in those symptoms initially targeted for treatment. Side effects of the medication should also be determined, with particular attention to those that patients may be reluctant to disclose (e.g., sexual dysfunction). Patients who are intolerant of a particular medication can, of course, be switched to another agent. It may be useful to complete symptom-rating scales (see Tables 6.4., 6.5.) in order to help quantify response to medication.[50-52]

When there is a poor response to medication, it is important to optimise dosage and duration of the medication. Although the dose-response relationship of the SSRIs has not been as well studied in the anxiety disorders as in depression, there appears to be a relatively flat dose-response curve.[53] Despite this, some patients may fail to respond to the standard initial starting dose, but do well at higher doses.[54] There is increasing awareness that some patients may be rapid metabolisers of antidepressant medication and, therefore, require significantly higher doses than usual.[55-58] Elderly patients generally require lower doses than do younger adults, and are generally more sensitive to medication side effects.[25]

Furthermore, response to SSRIs in these disorders may take six to eight weeks or even longer. It is important to give each patient a trial of medication that is of adequate duration.

STEP 5: MAINTENANCE OF RESPONSE AND AUGMENTATION STRATEGIES FOR PARTIAL RESPONSE

At the end of a clinical trial of optimal dose and duration, patients should be thoroughly re-assessed. There is growing recognition of the importance of residual anxiety symptoms in causing disability and predicting relapse, and of the consequent necessity of aiming for remission of symptoms as the endpoint of treatment.[59-61]

When the patient has a good response to medication, it is important to reinforce the necessity of continuing the medication at the therapeutic dose despite this improvement. Guidelines for maintenance therapy of anxiety disorders have become increasingly conservative, favouring longer courses of medication, in view of the safety of modern antidepressant agents and the likelihood of relapse in patients with an untreated chronic illness. In panic disorder and social anxiety disorder it is not unreasonable to continue medication for at least a year before gradual tapering.[44,59,60] Gradual tapering off of antidepressants is recommended due to the risk of antidepressant withdrawal.[62] Cognitive-behavioural therapy may be useful prior to beginning and during medication withdrawal in order to maintain gains, although more research on the optimal combination and sequencing of pharmacotherapy and psychotherapy in these disorders is needed.[63,64]

Continued on page 60

Table 6.4. Liebowitz Social Anxiety Scale (for social anxiety disorder)

Use the following key to answer each question:		
Fear or anxiety: **0** = none **1** = mild **2** = moderate **3** = severe	**Avoidance:** **0** = never (0%) **1** = occasionally (1-33%) **2** = often (33-67%) **3** = usually (67-100%)	
	Fear or anxiety	**Avoidance**
1 Telephoning in public.		
2 Participating in small groups.		
3 Eating in public places.		
4 Drinking with others in public places.		
5 Talking to people in authority.		
6 Acting, performing, giving a talk in front of an audience.		
7 Going to a party.		
8 Working while being observed.		
9 Writing while being observed.		
10 Calling someone you don't know very well.		
11 Talking with people you don't know very well.		
12 Meeting strangers.		
13 Urinating in a public bathroom.		
14 Entering a room when others are already seated.		
15 Being the centre of attention.		
16 Speaking up at a meeting.		
17 Taking a test.		
18 Expressing disagreement or disapproval to people you don't know very well.		
19 Looking at people you don't know very well in the eyes.		
20 Giving a report to a group.		
21 Trying to pick up someone.		
22 Returning goods to a store.		
23 Giving a party.		
24 Resisting a high-pressure salesperson.		
Total score (max. = 144)..... Suggested interpretation: 55-65 = moderate social phobia 65-80 = marked social phobia 80-95 = severe social phobia 95 and above = very severe social phobia		

Table 6.5. Panic disorder severity scale (PDSS)

Several of the questions refer to panic attacks and limited symptom attacks.
For this questionnaire, panic attacks are defined as a sudden rush (ie, peaking in 10 minutes) of fear or discomfort, accompanied by at least four of the symptoms listed below:

- Rapid or pounding heartbeat
- Sweating
- Trembling or shaking
- Breathlessness
- Feeling of choking
- Chest pain or discomfort
- Nausea
- Dizziness or faintness
- Feelings of unreality
- Numbness or tingling
- Chills or hot flushes
- Fear of losing control or going crazy
- Fear of dying

1. How many panic and limited symptom attacks did you have during the week?
0 = No panic or limited symptom episodes
1 = Mild: no full panic attacks and no more than one limited symptom attack/day
2 = Moderate: one or two full panic attacks and/or multiple limited symptom attacks/day
3 = Severe: more than two full attacks, but not more than one/day on average
4 = Extreme: full panic attacks occurred more than once a day, more days than not

2. If you had any panic attacks during the past week, how distressing (uncomfortable, frightening) were they while they were happening? (If you had more than one, give an average rating. If you didn't have any panic attacks, but did have limited symptom attacks, answer for the limited symptom attacks.)
0 = Not at all distressing, or no panic or limited symptom attacks during the past week
1 = Mildly distressing (not too intense)
2 = Moderately distressing (intense, but still manageable)
3 = Severely distressing (very intense)
4 = Extremely distressing (extreme distress during all attacks)

3. During the past week, how much have you worried or felt anxious about when your next panic attack would occur or about fears related to the attacks (for example, that they could mean you have physical or mental health problems or could cause you social embarrassment)?
0 = Not at all
1 = Occasionally or only mildly
2 = Frequently or moderately
3 = Very often or to a very disturbing degree
4 = Nearly constantly and to a disabling extent

4. During the past week were there any places or situations (eg, public transportation, movie theatres, crowds, bridges, tunnels, shopping malls, being alone) you avoided, or felt afraid of (uncomfortable in, wanted to avoid or leave), because of fear of having a panic attack? Are there any other situations that you would have avoided or been afraid of if they had come up during the week, for the same reason? If yes to either question, please rate your level of fear and avoidance this past week.
0 = None: no fear or avoidance
1 = Mild: occasional fear and/or avoidance, but I could usually confront or endure the situation. There was little or no modification of my lifestyle due to this.
2 = Moderate: noticeable fear and/or avoidance, but still manageable. I avoided some situations, but I could confront them with a companion. There was some modification of my lifestyle because of this, but my overall functioning was not impaired.
3 = Severe: extensive avoidance. Substantial modification of my lifestyle was required to accommodate the avoidance, making it difficult to manage usual activities.
4 = Extreme: pervasive disabling fear and/or avoidance. Extensive modification in my lifestyle was required such that important tasks were not performed.

Table 6.5. (continued)

5. During the past week, were there any activities (eg, physical exertion, sexual relations, taking a hot shower or bath, drinking coffee, watching an exciting or scary movie) that you avoided, or felt afraid of (uncomfortable doing, wanted to avoid or stop), because they caused physical sensations like those you feel during panic attacks or that you were afraid might trigger a panic attack? Are there any other activities that you would have avoided or been afraid of if they had come up during the week for that reason? If you answered yes to either question, please rate your level of fear and avoidance of those activities this past week.

0 = No fear or avoidance of situations or activities because of distressing physical sensations
1 = Mild: occasional fear and/or avoidance, but usually I could confront or endure with little distress activities that cause physical sensations. There was little modification of my lifestyle due to this.
2 = Moderate: noticeable avoidance but still manageable. There was definite, but limited, modification of my lifestyle such that my overall functioning was not impaired.
3 = Severe: extensive avoidance. There was substantial modification of my lifestyle or interference in my functioning.
4 = Extreme: pervasive and disabling avoidance. There was extensive modification in my lifestyle due to this such that important tasks or activities were not performed.

6. During the past week, how much did the above symptoms altogether (panic and limited symptom attacks, worry about attacks, and fear of situations and activities because of attacks) interfere with your ability to work or carry out your responsibilities at home? (If your work or home responsibilities were less than usual this past week, answer how you think you would have done if the responsibilities had been usual.)

0 = No interference with work or home responsibilities
1 = Slight interference with work or home responsibilities, but I could do nearly everything I could if I didn't have these problems.
2 = Significant interference with work or home responsibilities, but I still could manage to do the things I needed to do.
3 = Substantial impairment in work or home responsibilities; there were many important things I couldn't do because of these problems.
4 = Extreme, incapacitating impairment such that I was essentially unable to manage any work or home responsibilities.

7. During the past week, how much did panic and limited symptom attacks, worry about attacks and fear of situations and activities because of attacks interfere with your social life? (If you didn't have many opportunities to socialise this past week, answer how you think you would have done if you did have opportunities.)

0 = No interference
1 = Slight interference with social activities, but I could do nearly everything I could if I didn't have these problems.
2 = Significant interference with social activities, but I could manage to do most things if I made the effort.
3 = Substantial impairment in social activities; there are many social things I couldn't do because of these problems.
4 = Extreme, incapacitating impairment, such that there was hardly anything social I could do.

Total score (max. = 28):_____

Suggested interpretation without agoraphobia:
0-1 = normal; 2-5 = borderline; 6-9 = slightly ill; 10-13 = moderately ill; 14 and above = markedly ill.

Suggested interpretation with agoraphobia:
0-2 = normal; 3-7 = borderline; 8-10 = slightly ill; 11-15 = moderately ill; 16 and above = markedly ill

As per cutoffs in: Furukawa TA, Katherine Shear M, Barlow DH, *at al.* Evidence-based guidelines for interpretation of the Panic Disorder Severity Scale. Depression and Anxiety. 2009 Oct;26(10):922-9.

When there is a partial response despite an optimum trial of medication, it may be useful to consider an augmenting agent. In general, another first-line agent from a different class could be considered for augmentation, however neither augmentation nor switching strategies in these conditions has been well researched.[26] Augmentation offers the advantage of retaining any possible gains from the first agent, but the potential disadvantages of polypharmacy (more side effects, drug interactions).[65,66] Of all the augmentation strategies in the treatment of the anxiety disorders, however, arguably the most important is augmentation of pharmacotherapy with additional psychotherapy.[8,44,67]

In panic disorder, high-potency benzodiazepines have been described as useful in treatment-resistant panic disorder.[42] These agents (particularly slow-release agents or those with a longer half-life) may be expected to reduce anxiety secondary to antidepressants and to combat the primary disorder. However, the potential for dependence and rebound anxiety must be borne in mind. The anticonvulsants gabapentin and pregabalin do not have dependence potential, and have shown some efficacy as monotherapy in panic disorder.[25,68,69] Therefore, these agents are another theoretical possibility for use as augmenting agents.[25,49,68] Another possibility is the use of pindolol to augment an SSRI, a strategy found useful in a preliminary controlled trial in panic disorder.[70,71] Finally, there is some evidence to support the cautious use of some of the atypical antipsychotics; limited data exist currently for aripiprazole, olanzapine and risperidone.[42,49,68] Specialist consultation may be advisable when augmentation seems indicated.

In social anxiety disorder, given its efficacy as monotherapy, augmentation with clonazepam is again a consideration.[65] Nevertheless, this again poses the risk of benzodiazepine dependence. The anticonvulsants gabapentin and pregabalin also showed some efficacy as monotherapy in social anxiety disorder.[25,72] They do not have dependence potential, and so are another theoretical possibility for use as augmenting agents. Nevertheless, there remains a paucity of research on augmentation strategies in social anxiety disorder.

STEP 6: FAILURE TO RESPOND

When anxiety disorders do not respond to a clinical trial of optimal dose and duration, it is useful to re-assess a number of factors. The presence of certain features may impact on the choice of the subsequent intervention.

a. **Adherence:** Clinicians often overestimate the adherence of their patients, and it is often useful to check with patients and their families whether medication is being taken as prescribed. Many patients worry that medication is addictive or a "crutch".
b. **Comorbid substance use:** In the presence of active alcohol or substance use, it may be necessary to shift the emphasis of treatment towards a substance-use disorder as the primary diagnosis, with the anxiety as a secondary problem. Detoxification may be a necessary first step in the management of these patients.[33] Anxiety may also be present during the withdrawal phase from a number of substances, including cannabinoids, stimulants and opioids.
c. **Comorbid personality disorders:** Although antidepressants may be useful, additional interventions, such as psychotherapy, may be helpful in patients with chronic anxiety and comorbid personality disorder. While improvement in anxiety symptoms may reduce maladaptive behaviour in patients with comorbid personality disorder, there are other patients (e.g., those with borderline personality disorder) in whom the personality disorder itself may need to be a major target of treatment.[73]
d. **Underlying medical disorder:** Anxious patients who fail to respond to medication should be thoroughly re-assessed for an underlying medical disorder. A range of different medical disorders may lead to chronic anxiety, including endocrine disorders (e.g., hyperthyroidism), respiratory disorders (e.g., chronic obstructive pulmonary disorder), cardiac disorders (e.g., congestive heart failure) and others.[74] If present, such disorders naturally require specific intervention. When using a benzodiazepine in patients with liver dysfunction, consider using those metabolised only by conjugation (e.g., lorazepam, oxazepam) so as to avoid accumulation.
e. **Pharmacokinetic issues:** Drug-drug interactions may result in a subtherapeutic dose of the prescribed antidepressant.
f. **Psychosocial issues:** Psychosocial circumstances that continue to complicate the course of an anxiety disorder need to

be assessed, as these may necessitate appropriate intervention. Loss or separation may precipitate panic disorder, and this may need to be addressed. Ongoing avoidance patterns, such as avoidance of feared social situations in social anxiety disorder, may need to be specifically addressed.

STEP 7: TREATMENT RESISTANCE

After the failure of an adequate clinical trial of medication in a patient where re-assessment sheds no light on any further unresolved factors, a different agent should be used. It is often advisable to switch classes of medication. It is also possible that switching from one SSRI to another may be useful.

Some medications may be particularly useful in cases of treatment-resistant anxiety disorders. Venlafaxine has been suggested to be useful in patients with social anxiety disorder who have failed to respond to SSRIs.[46] The classical, irreversible MAOIs, despite necessitating measures such as a specialised diet, remain a useful resource for patients with panic disorder or social anxiety disorder who have not responded to other more commonly used classes of medication.[17,75] Finally, augmentation strategies (as outlined above) can sometimes be useful in patients who have not responded to multiple single agents. Repetitive transcranial magnetic stimulation (rTMS) may be efficacious and well-tolerated in generalised anxiety disorder, however the evidence supporting this particular intervention for panic disorder and social anxiety disorder is currently inconclusive.[76-78]

If all avenues have been thoroughly explored, a second opinion by an expert is indicated. Medication trials that ended prematurely or that did not use optimal dosing can be repeated. It may ultimately be necessary to revert to the regimen on which the patient demonstrated the best response.

ADDITIONAL READING

1. Combs H, Markman J. Anxiety disorders in primary care. Med Clin North Am. 2014;98(5):1007-23.
2. Baldwin DS, Anderson IM, Nutt DJ, *et al*. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: A revision of the 2005 guidelines from the British Association for Psychopharmacology. J Psychopharmacol. 2014;28(5):403-39.3.
3. Katzman MA, Bleau P, Blier P, *et al*. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. BMC Psychiatry. 2014;14 Suppl 1:S1.
4. Bandelow B, Zohar J, Hollander E, *et al*. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and posttraumatic stress disorders – first revision. World J Biol Psychiatry. 2008;9(4):248-312.
5. Bandelow B, Baldwin DS, Zwanzger P. Pharmacological treatment of panic disorder. Mod Trends Pharmacopsychiatry. 2013;29:128-43.
6. Freire RC, Machado S, Arias-Carrion O, *et al*. Current pharmacological interventions in panic disorder. CNS Neurol Disord Drug Targets. 2014;13(6):1057-65.
7. Masdrakis VG, Turic D, Baldwin DS. Pharmacological treatment of social anxiety disorder. Mod Trends Pharmacopsychiatry. 2013;29:144-53.
8. Davis ML, Smits JA, Hofmann SG. Update on the Efficacy of Pharmacotherapy for Social Anxiety Disorder: A Meta-Analysis. Expert Opin Pharmacother. 2014;15(16):2281-91.
9. Dell'osso B, Lader M. Do benzodiazepines still deserve a major role in the treatment of psychiatric disorders? A critical reappraisal. Eur Psychiatry. 2013;28(1):7-20.
10. Latas M, Milovanovic S. Personality disorders and anxiety disorders: What is the relationship? Curr Opin Psychiatry. 2014;27(1):57-61.
11. Andrews G, Bell C, Boyce P, *et al*. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of panic disorder, social anxiety disorder and generalised anxiety disorder. Aust N Z J Psychiatry. 2018 Dec;52(12):1109-72.

REFERENCES

1. Steel Z, Marnane C, Iranpour C, *et al*. The Global Prevalence of Common Mental Disorders: A Systematic Review and Meta-Analysis 1980-2013. Int J Epidemiol. 2014;43(2):476-93.
2. Bandelow B, Michaelis S. Epidemiology of anxiety disorders in the 21st century. Dialogues Clin Neurosci. 2015 Sep;17(3):327-35.
3. Combs H, Markman J. Anxiety disorders in primary care. Med Clin North Am. 2014;98(5):1007-23.
4. DiLuca M, Olesen J. The cost of brain diseases: A burden or a challenge? Neuron. 2014 Jun;82(6):1205-8.
5. Bandelow B, Michaelis S, Wedekind D. Treatment of anxiety disorders. Dialogues Clin Neurosci. 2017 Jun;19(2):93-107.
6. Konnopka A, König H. Economic Burden of Anxiety Disorders: A Systematic Review and Meta-Analysis. PharmacoEconomics. 2020 Jan;38(1):25-37.
7. Cuijpers P, Sijbrandij M, Koole SL, *et al*. Adding Psychotherapy to Antidepressant Medication

in Depression and Anxiety Disorders: A Meta-Analysis. World Psychiatry. 2014;13(1):56-67.
8. Pompoli A, Furukawa TA, Imai H, *et al.* Psychological Therapies for Panic Disorder with or without Agoraphobia in Adults: A Network Meta-Analysis. Cochrane Database Syst Rev. 2016(4):CD011004.
9. Wersebe H, Sijbrandij M, Cuijpers P. Psychological Group-Treatments of Social Anxiety Disorder: A Meta-Analysis. PLoS One. 2013;8(11):79034.
10. Sanchez-Meca J, Rosa-Alcazar AI, Marin-Martinez F, *et al*. Psychological Treatment of Panic Disorder with or without Agoraphobia: A Meta-Analysis. Clin Psychol Rev. 2010;30(1):37-50.
11. Bandelow B, Michaelis S, Wedekind D. Treatment of anxiety disorders. Dialogues Clin Neurosci. 2017 Jun;19(2):93-107.
12. Cuijpers P, Cristea IA, Karyotaki E, *et al*. How effective are cognitive behavior therapies for major depression and anxiety disorders? A meta-analytic update of the evidence. World Psychiatry. 2016 Oct;15(3):245-58.
13. Carpenter JK, Andrews LA, Witcraft SM, *et al*. Cognitive Behavioral Therapy for Anxiety and Related Disorders: A Meta-Analysis of Randomized Placebo-Controlled Trials. Depress Anxiety. 2018 Jun;35(6):502-14.
14. Davies EB, Morriss R, Glazebrook C. Computer-Delivered and Web-Based Interventions to Improve Depression, Anxiety, and Psychological Well-Being of University Students: A Systematic Review and Meta-Analysis. J Med Internet Res. 2014 May 16;16(5):e130.
15. Zhao S, Sampson S, Xia J, *et al.* Psychoeducation (brief) for people with serious mental illness. Cochrane Database Syst Rev. 2015(4):CD010823.
16. Sin J, Jordan CD, Barley EA, *et al*. Psychoeducation for siblings of people with severe mental illness. Cochrane Database Syst Rev. 2015(5):CD010540.
17. Davis ML, Smits JA, Hofmann SG. Update on the Efficacy of Pharmacotherapy for Social Anxiety Disorder: A Meta-Analysis. Expert Opin Pharmacother. 2014;15(16):2281-91.
18. Baker HJ, Waite P. The identification and psychological treatment of panic disorder in adolescents: A survey of CAMHS clinicians. Child Adolesc Ment Health. 2020 Sep;25(3):135-42.
19. Oyebode F. Sims' Symptoms in the Mind: Textbook of Descriptive Psychopathology E-Book. Elsevier Health Sciences; 2018. 347.
20. Lai HMX, Cleary M, Sitharthan T, *et al*. Prevalence of Comorbid Substance Use, Anxiety and Mood Disorders in Epidemiological Surveys, 1990-2014: A Systematic Review and Meta-Analysis. Drug Alcohol Depend. 2015 Sep;154:1-13.
21. Anker JJ, Kushner MG. Co-occurring alcohol use disorder and anxiety: Bridging psychiatric, psychological, and neurobiological perspectives. Alcohol Res Curr Rev. 2019;40(1):03.
22. Meuret AE, Tunnell N, Roque A. Anxiety disorders and medical comorbidity: Treatment implications. Adv Exp Med Biol. 2020;1191:237-61.
23. Klevebrant L, Frick A. Effects of Caffeine on Anxiety and Panic Attacks in Patients with Panic Disorder: A Systematic Review and Meta-Analysis. Gen Hosp Psychiatry. 2022 Jan;74:22-31.
24. Kanwar A, Malik S, Prokop LJ, *et al*. The Association between Anxiety Disorders and Suicidal Behaviors: A Systematic Review and Meta-Analysis. Depress Anxiety. 2013;30(10):917-29.
25. Bandelow B. Current and novel psychopharmacological drugs for anxiety disorders. Adv Exp Med Biol. 2020;1191:347-65.
26. Baldwin DS, Anderson IM, Nutt DJ, *et al*. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: A revision of the 2005 guidelines from the British Association for Psychopharmacology. J Psychopharmacol Oxf Engl. 2014 May;28(5):403-39.
27. Shinfuku M, Kishimoto T, Uchida H, *et al*. Effectiveness and Safety of Long-Term Benzodiazepine Use in Anxiety Disorders: A Systematic Review and Meta-Analysis. Int Clin Psychopharmacol. 2019 Sep;34(5):211-21.
28. Longo LP, Addiction JB, Part I. Benzodiazepines – side effects, abuse risk and alternatives. Am Fam Physician. 2000;61(7):2121-8.
29. Sani G, Tondo L, Undurraga J, *et al*. Melancholia: Does this ancient concept have contemporary utility? Int Rev Psychiatry Abingdon Engl. 2020 Sep;32(5–6):466-70.
30. Sneed JR, Reinlieb ME, Rutherford BR, *et al*. Antidepressant treatment of melancholia in older adults. Am J Geriatr Psychiatry Off J Am Assoc Geriatr Psychiatry. 2014 Jan;22(1):46-52.
31. Geduldig ET, Kellner CH. Electroconvulsive therapy in the elderly: New findings in geriatric depression. Curr Psychiatry Rep. 2016 Apr;18(4):40.
32. Cipriani A, Furukawa TA, Salanti G, *et al*. Comparative Efficacy and Acceptability of 21 Antidepressant Drugs for the Acute Treatment of Adults with Major Depressive Disorder: A Systematic Review and Network Meta-Analysis. The Lancet. 2018 Apr;391(10128):1357-66.
33. Ipser JC, Wilson D, Akindipe TO, *et al*. Pharmacotherapy for anxiety and comorbid alcohol use disorders. Cochrane Database Syst Rev. 2015(1):CD007505.
34. Fitton CA, Steiner MFC, Aucott L, *et al*. In Utero Exposure to Antidepressant Medication and Neonatal and Child Outcomes: A Systematic Review. Acta Psychiatr Scand. 2020 Jan; 141(1):21-33.

35. Grigoriadis S, Vonderporten EH, Mamisashvili L, *et al*. Prenatal Exposure to Antidepressants and Persistent Pulmonary Hypertension of the Newborn: Systematic Review and Meta-Analysis. BMJ. 2014;348:6932.
36. Okun ML, Ebert R, Saini B. A review of sleep-promoting medications used in pregnancy. Am J Obstet Gynecol. 2015 Apr 1;212(4):428-41.
37. Grigoriadis S, Graves L, Peer M, *et al*. Pregnancy and Delivery Outcomes Following Benzodiazepine Exposure: A Systematic Review and Meta-Analysis. Can J Psychiatry Rev Can Psychiatr. 2020 Dec;65(12):821-34.
38. Andrews G, Bell C, Boyce P, *et al*. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of panic disorder, social anxiety disorder and generalised anxiety disorder. Aust N Z J Psychiatry. 2018 Dec;52(12):1109-72.
39. Jakubovski E, Johnson JA, Nasir M, *et al*. Systematic Review and Meta-Analysis: Dose-Response Curve of SSRIs and SNRIs in Anxiety Disorders. Depress Anxiety. 2019 Mar;36(3): 198-212.
40. Williams T, Hattingh CJ, Kariuki CM, *et al*. Pharmacotherapy for social anxiety disorder (SAnD). Cochrane Database Syst Rev. 2017(10): CD001206.
41. Williams T, McCaul M, Schwarzer G, *et al*. Pharmacological Treatments for Social Anxiety Disorder in Adults: A Systematic Review and Network Meta-Analysis. Acta Neuropsychiatr. 2020 Aug;32(4):169-76.
42. Freire RC, Machado S, Arias-Carrion O, *et al*. Current pharmacological interventions in panic disorder. CNS Neurol Disord Drug Targets. 2014;13(6):1057-65.
43. Bighelli I, Trespidi C, Castellazzi M, *et al*. Antidepressants and benzodiazepines for panic disorder in adults. Cochrane Database Syst Rev. 2016(9):CD011567.
44. National Institute for Health and Care Excellence. Generalised Anxiety Disorder and Panic Disorder in Adults [Internet]. [London]: NICE; 2011 [updated 2020 Jun; cited 2022 May 28]. (Clinical guideline [CG113]). Available from: https://www.nice.org.uk/guidance/cg113.
45. Steenen SA, van Wijk AJ, van der Heijden GJ, *et al*. Propranolol for the Treatment of Anxiety Disorders: Systematic Review and Meta-Analysis. J Psychopharmacol. 2016 Feb;30(2):128-39.
46. Williams T, Hattingh CJ, Kariuki CM, *et al*. Pharmacotherapy for social anxiety disorder (SAnD). Cochrane Database Syst Rev. 2017(10): CD001206.
47. Starcevic V. The reappraisal of benzodiazepines in the treatment of anxiety and related disorders. Expert Rev Neurother. 2014;14(11):1275-86.
48. Gomez AF, Barthel AL, Hofmann SG. Comparing the Efficacy of Benzodiazepines and Serotonergic Anti-Depressants for Adults with Generalized Anxiety Disorder: A Meta-Analytic Review. Expert Opin Pharmacother. 2018 May 24;19(8):883-94.
49. Masdrakis VG, Baldwin DS. Anticonvulsant and antipsychotic medications in the pharmacotherapy of panic disorder: A structured review. Ther Adv Psychopharmacol. 2021 Jan; 11:204512532110023.
50. Romba C, Lavigne J, Walkup J, *et al*. Measurement-based care in the treatment of anxiety. Child Adolesc Psychiatr Clin N Am. 2020 Oct; 29(4):645-61.
51. Liebowitz MR. Social phobia. Mod Probl Pharmacopsychiatry. 1987;22:141-73.
52. Furukawa TA, Shear MK, Barlow DH, *et al*. Evidence-Based Guidelines for Interpretation of the Panic Disorder Severity Scale. Depress Anxiety. 2009;26(10):922-9.
53. Baldwin DS, Anderson IM, Nutt DJ, *et al*. Evidence-based pharmacological treatment of anxiety disorders, posttraumatic stress disorder and obsessive compulsive disorder: A revision of the 2005 guidelines from the British Association for Psychopharmacology. J Psychopharmacol. 2014;28(5):403-39.
54. Jakubovski E, Johnson JA, Nasir M, *et al*. Systematic Review and Meta-Analysis: Dose-Response Curve of SSRIs and SNRIs in Anxiety Disorders. Depress Anxiety. 2019 Mar; 36(3):198-212.
55. Fabbri C, Crisafulli C, Calabrò M, *et al*. Progress and prospects in pharmacogenetics of antidepressant drugs. Expert Opin Drug Metab Toxicol. 2016 Oct 2;12(10):1157-68.
56. García-González J, Tansey KE, Hauser J, *et al*. Pharmacogenetics of antidepressant response: A polygenic approach. Prog Neuropsychopharmacol Biol Psychiatry. 2017 Apr 3;75:128-34.
57. Niitsu T, Fabbri C, Bentini F, *et al*. Pharmacogenetics in Major Depression: A Comprehensive Meta-Analysis. Prog Neuropsychopharmacol Biol Psychiatry. 2013;45:183-94.
58. Gvozdic K, Brandl EJ, Taylor DL, *et al*. Genetics and personalized medicine in antidepressant treatment. Curr Pharm Des. 2012;18(36):5853-78.
59. Caldirola D, Alciati A, Daccò S, *et al*. Relapse prevention in panic disorder with pharmacotherapy: Where are we now? Expert Opin Pharmacother. 2020 Sep 21;21(14):1699-711.
60. Batelaan NM, Bosman RC, Muntingh A, *et al*. Risk of Relapse After Antidepressant Discontinuation in Anxiety Disorders, Obsessive-Compulsive Disorder, and Post-Traumatic Stress Disorder: Systematic Review and Meta-Analysis of Relapse Prevention Trials. BMJ. 2017 Sep 13;358:j3927.
61. Van Leeuwen E, van Driel ML, Horowitz MA, *et al*. Approaches for discontinuation versus

continuation of long-term antidepressant use for depressive and anxiety disorders in adults. Cochrane Database Syst Rev. 2021(4):CD013495.
62. Fava GA, Cosci F. Understanding and managing withdrawal syndromes after discontinuation of antidepressant drugs. J Clin Psychiatry. 2019 Nov 26;80(6).
63. Bandelow B, Reitt M, Röver C, *et al*. Efficacy of Treatments for Anxiety Disorders: A Meta-Analysis. Int Clin Psychopharmacol. 2015 Jul; 30(4):183-92.
64. Bandelow B, Reitt M, Röver C, *et al*. Efficacy of Treatments for Anxiety Disorders: A Meta-Analysis. Int Clin Psychopharmacol. 2015 Jul; 30(4):183-92.
65. Pollack MH, Van Ameringen M, Simon NM, *et al*. A double-blind randomized controlled trial of augmentation and switch strategies for refractory social anxiety disorder. Am J Psychiatry. 2014;171(1):44-53.
66. Fava M. Augmentation and combination strategies in treatment-resistant depression. J Clin Psychiatry. 2001;18:4-11.
67. Zhou X, Teng T, Zhang Y, *et al*. Comparative Efficacy and Acceptability of Antidepressants, Psychotherapies, and Their Combination for Acute Treatment of Children and Adolescents with Depressive Disorder: A Systematic Review and Network Meta-Analysis. Lancet Psychiatry. 2020 Jul;7(7):581-601.
68. Katzman MA, Bleau P, Blier P, *et al*. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. BMC Psychiatry. 2014;14 Suppl 1:S1.
69. Garakani A, Murrough JW, Freire RC, *et al*. Pharmacotherapy of anxiety disorders: Current and emerging treatment options. Front Psychiatry. 2020;11.
70. Hirschmann S, Dannon PN, Iancu I, *et al*. Pindolol Augmentation in Patients with Treatment-Resistant Panic Disorder: A Double-Blind, Placebo-Controlled Trial. J Clin Psychopharmacol. 2000;20(5):556-9.
71. Cojocariu SA, Maștaleru A, Sascău RA, *et al*. Neuropsychiatric consequences of lipophilic beta-blockers. Medicina (Mex). 2021 Feb 9;57(2):155.
72. Kawalec P, Cierniak A, Pilc A, *et al*. Pregabalin for the treatment of social anxiety disorder. Expert Opin Investig Drugs. 2015 Apr;24(4):585-94.
73. Latas M, Milovanovic S. Personality disorders and anxiety disorders: What is the relationship? Curr Opin Psychiatry. 2014;27(1):57-61.
74. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. Washington, DC: American Psychiatric Publishing; 2013.
75. Menkes D, Bosanac P, Castle D. MAOIs – does the evidence warrant their resurrection? Australas Psychiatry. 2016 Aug;24(4):371-3.
76. Li H, Wang J, Li C, *et al*. Repetitive transcranial magnetic stimulation (rTMS) for panic disorder in adults. Cochrane Database Syst Rev. 2014(9):CD009083.
77. Cui H, Jiang L, Wei Y, *et al*. Efficacy and Safety of Repetitive Transcranial Magnetic Stimulation for Generalised Anxiety Disorder: A Meta-Analysis. Gen Psychiatry. 2019 Sep;32(5):e100051.
78. Paes F, Baczynski T, Novaes F, *et al*. Repetitive transcranial magnetic stimulation (rTMS) to treat social anxiety disorder: Case reports and a review of the literature. Clin Pract Epidemiol Ment Health CP EMH. 2013 Oct 31;9:180-8.

7: Generalised Anxiety Disorder

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In this chapter we focus on generalised anxiety disorder (GAD). There have been important recent advances in the nosology and treatment of this disorder. In particular, there is increasing evidence that patients with GAD and mixed anxiety-depression frequently present in primary care settings,[1-3] and the ICD-11 provides fairly user-friendly guidelines for the diagnosis of GAD (see Table 7.1.). A few simple points can perhaps be made to help conceptualise GAD. In primary care practice, generalised anxiety disorder can perhaps be viewed as a "tension disorder". This is a useful term insofar as it crosses the boundary between psychic symptoms (worries, feeling keyed up, irritability) and somatic complaints (muscle tension, restlessness, insomnia). While GAD patients may not present with "worries", they often describe themselves as "worriers" – worry may represent an avoidance behaviour that is used to diminish tension (analogous to the way that agoraphobia may develop after panic attacks).

The algorithm presented here (see Figure 7.1.) provides a step-by-step approach to the pharmacotherapy of GAD in adults, based on our reading of the research literature. It is important to mention at the outset, however, that psychotherapy approaches may be a first-line intervention in some GAD patients and should be considered in all patients with this disorder.[4-9] In addition, psycho-education is of the utmost importance, particularly in the initial stages of treatment, and should address the direct effects of anxiety on the life of the patient, as well as possible effects on family members.[8,10,11]

Figure 7.1. Algorithm for pharmacotherapy of GAD

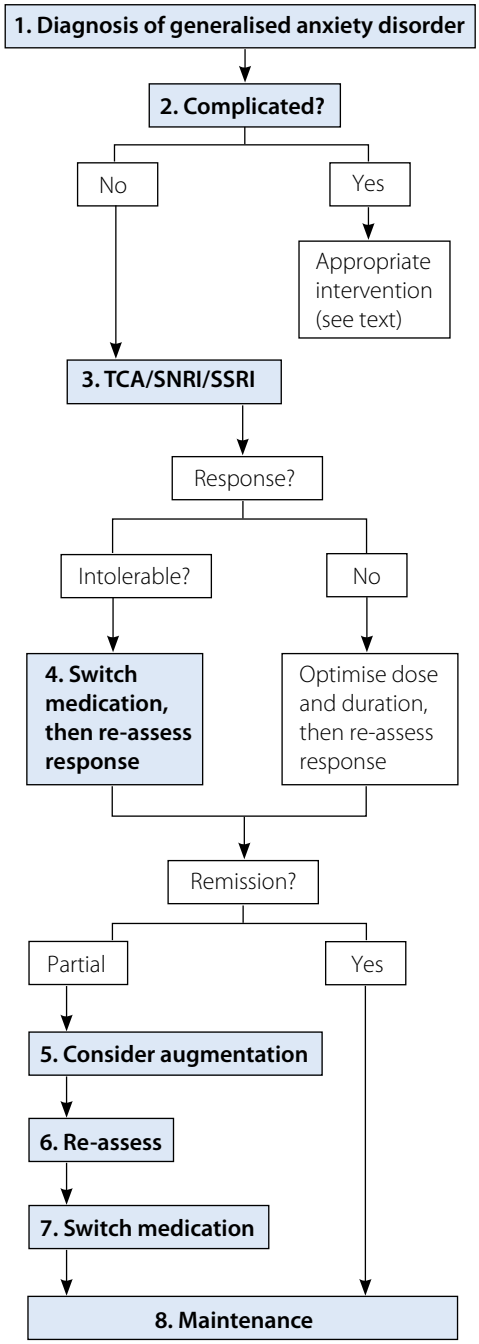

Table 7.1. Diagnostic guidelines for generalised anxiety disorder (adapted from ICD-11)

1. Marked symptoms of anxiety manifested by either general apprehensiveness (not restricted to a particular environmental circumstance, i.e., 'free-floating anxiety'), or excessive worry about negative events occurring in several different aspects of everyday life (e.g., work, finances, health, family)
2. The anxiety and worry are accompanied by other characteristic symptoms, including: • Restlessness, nervousness or feeling 'on edge'. • Sympathetic autonomic overactivity (evidenced by nausea and/or abdominal distress, heart palpitations, sweating, trembling, shaking, dry mouth) • Difficulty concentrating or mind going blank • Irritability • Muscle tension or motor restlessness • Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep)
3. The symptoms are not transient and persist for at least several months, and are present for more days than not
4. The anxiety, worry or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
5. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism).
6. The disturbance is not better explained by another mental disorder.

STEP 1: DIAGNOSIS OF GENERALISED ANXIETY DISORDER

GAD is characterised by chronic, uncontrollable and excessive worry, which is accompanied by a range of somatic symptoms. Making the correct diagnosis is essential. Given that GAD often presents with somatic symptoms and comorbid psychiatric disorders, the diagnosis is frequently overlooked.[12,13] On the other hand, improvements in the nosology and treatment of GAD now make it useful to establish whether diagnostic criteria for this disorder are met.

Particular attention should be paid to the evaluation of symptoms that are chosen as targets for pharmacotherapy and to symptoms that may point to the presence of other psychiatric disorders. It is also useful to determine the severity of GAD symptoms, using a scale such as the Hamilton Anxiety Scale.[14-16] It is possible that the situation in GAD mirrors that in depression, where less severe forms of the disorder respond equally well to pharmacotherapy and to psychotherapy.

It is also necessary to rule out the presence of comorbid psychiatric and medical disorders. Mood disorders, such as depression and dysthymia, and other anxiety disorders are common in patients with GAD.[17-20] In addition, attention should be paid to the possibility of comorbid somatisation disorder or substance abuse, dependence, or withdrawal.[21,22] In particular, excessive alcohol or caffeine use may contribute to chronic anxiety symptoms and should be excluded.[23,24] Children with pervasive anxiety likely deserve specialist evaluation before a diagnosis of GAD is made.

STEP 2: COMPLICATIONS IN DIAGNOSIS IMPACTING PHARMACOTHERAPY

Several factors may complicate GAD, thus impacting on decisions about pharmacotherapy and other interventions. The most important of these factors, along with their treatment implications, are listed below:

a. **Geriatric patients:** Research indicates that GAD in the elderly is not uncommon and is often accompanied by depression.[25,26] Benzodiazepines (particularly in high doses or those with long half-lives) should be prescribed only with great caution in this population, given the possibility of drug accumulation and consequent adverse effects, such as motor vehicle accidents, falls, and fractures.[27] In addition, dosages of many other psychotropic medications require adjustment in the elderly.
b. **Alcohol and/or substance use:** Alcohol and other substance-use disorders are

associated with an exacerbation of anxiety disorders. On the one hand, anxiety disorders may lead to use of alcohol and other substances in order to self-medicate anxiety. Thus, although it is generally advisable to detoxify patients prior to beginning pharmacotherapy, in some cases such pharmacotherapy is an integral part of the treatment of the secondary substance-use disorder.[28,29] There is some evidence that the SSRIs, in particular, may be useful for the treatment of anxiety disorders with a comorbid alcohol-use disorder, whereas benzodiazepines are relatively contraindicated in these patients.[28,30]

c. **Other comorbid disorders:** As noted earlier, there is a high rate of comorbidity among GAD, other anxiety disorders, and mood disorders.[7,17] GAD will often respond to the antidepressants that are used as first-line medication in these disorders, and these agents should therefore be prescribed initially. The presence of a comorbid personality disorder, however, predicts poorer treatment outcomes in GAD.[31]

d. **Pregnancy, lactation, menopause:** Pharmacotherapy should ideally be avoided during pregnancy and lactation. Nevertheless, where clinical considerations outweigh the risk of medication, such intervention should be considered after consultation with a specialist. Adverse pregnancy-outcome studies can be difficult to interpret and it is not always clear whether outcomes observed are due to medications themselves or confounders such as the underlying mental illness.[32-34] SSRIs are generally considered safe first-line agents in pregnancy and there is currently no conclusive evidence of an association between treatment with these agents and increased risk for malformations, preterm birth, low birth weight or small-for-gestational-age births.[33,35] However, fluoxetine and paroxetine use in early pregnancy may be associated with a small increased risk for cardiovascular malformations, and initiation of these agents should be avoided in the first trimester.[32,35] The risk of persistent pulmonary hypertension of the newborn has been shown to be increased for infants exposed to SSRIs in late pregnancy, although clinically the absolute risk is low.[32] Benzodiazepine use during pregnancy is not contra-indicated, but has been associated with an increased risk of cleft palate, preterm delivery and low birth weight.[36,37] If used, the lowest effective dose of the benzodiazepine should be prescribed for the shortest possible duration, and high peak concentrations should be avoided by dividing the daily dosage into two or three doses.

e. **Comorbid medical disorders and medications:** Clinicians need to be aware of the multiple interactions between medications used in the treatment of GAD and the treatment of other disorders, as well as of the impact of the medications' adverse effects on medical disorders.[38] Fortunately, certain SSRIs have relatively few interactions with other medications, and the SSRIs as a class are well tolerated in most medical disorders.

STEP 3: FIRST-LINE PHARMACOTHERAPY

Given the substantial comorbidity of GAD with depression and other disorders for which antidepressants are effective, expert consensus favours the use of one of these agents (specifically serotonin/noradrenaline re-uptake inhibitors, or selective serotonin re-uptake inhibitors).[7,8,39,40] However, a number of other agents may also be useful in patients with GAD.[41,42]

The TCAs have been shown effective in GAD in several controlled trials[43], although many of these agents have troublesome side-effect profiles.[44-46] There is also growing evidence that the SSRIs are useful in GAD, with similar effect sizes across class; a recent network meta-analysis suggests similar efficacy for escitalopram, sertraline and fluoxetine.[42] Venlafaxine and duloxetine are serotonin/noradrenaline re-uptake inhibitors that are as efficacious as first-line therapies.[7,42] Other classes of antidepressants, such as the classic mono-amine oxidase inhibitors (MAOIs – e.g., phenelzine) and noradrenergic and specific serotonergic antidepressants (NaSSA – e.g., mirtazapine), may also be effective in the treatment of GAD, although relatively less has been published on their use in this disorder.[42,47] Agomelatine, a melatonin agonist and 5HT2 antagonist, is another antidepressant that has shown efficacy in GAD, and that may be particularly useful in severe GAD.[42,48]

Pregabalin, an anticonvulsant acting at voltage-gated calcium channels, may be an alternative first-line treatment, and is efficacious and well-tolerated.[42,49,50] By contrast, randomised controlled trials investigating other anticonvulsants in GAD (such as tiagabine) have been negative.[46,51,52] There is a good deal of evidence for the efficacy of the benzodiazepines in GAD, as well as for their safety during long-term use, and some authors have recommended them as first-line agents.[53,54] Nevertheless, the high comorbidity of symptoms of depression in GAD and the significant difficulties experienced by many patients during benzodiazepine withdrawal, constitutes a strong argument against their first-line use. Benzodiazepines with longer half-lives or slow-release preparations may, however, be associated with fewer withdrawal problems.[55] Furthermore, hydroxyzine – an agent that is an antagonist at both the H1 and the 5HT2 receptor – has long been available, and while studies suggest efficacy and a lack of withdrawal symptoms after discontinuation in GAD[46,56], a Cochrane review emphasises significant methodological flaws in the relevant evidence base.[57]

Buspirone, a 5HT1A agonist, takes two to four weeks to begin working, and may be less helpful in patients recently treated with benzodiazepines.[58,59] Its advantage lies in its benign side-effect profile, the lack of dependence, and its efficacy in GAD.[42] Disadvantages include a lack of efficacy against the depressive symptoms often found in GAD, and a lack of efficacy in some trials.[42]

Although ß-blockers are often prescribed by general practitioners for anxiety symptoms, there seems insufficient evidence to include them as a first-line medication for GAD.[7] Similarly, alpha-2-adrenergic agonists such as clonidine and guanfacine have been researched as drugs for use in GAD, but there is lack of proven efficacy of these agents, as well as concerns about side effects such as hypotension and sedation.[46,60]

Recently, there has been attention on the potential use of cannabidiol and other cannabinoids in the treatment of anxiety.[61-63] While their anxiolytic effects seem promising, the quality of evidence for the role of cannabinoids in anxiety disorders is still very low.[61-63]

The role of ketamine and glutamate modulators as potential treatments for anxiety is an area that requires further research. Currently these agents don't have sufficient evidence for use as first-line agents in generalised anxiety.[64,65]

Kava extract is a herbal medicine that has shown promise for the treatment of anxiety, but it has not been studied rigorously enough in GAD, and its safety remains unclear.[66,67]

Similarly, we would be cautious about the use of low-dose antipsychotic medications in the treatment of chronic anxiety, despite data indicating that these agents may be useful for this indication, given their disadvantageous side-effect profiles (including tardive dyskinesia, weight gain and metabolic syndrome).[42,68,69]

STEP 4: ASSESS RESPONSE TO TREATMENT

The next step is to determine response to the medication. This is achieved by careful evaluation of change in symptoms initially targeted for treatment. These are typically excessive worry, various somatic symptoms, and consequent functional impairment. Determining the side effects of the medication is also important, as these may influence adherence. Gathering collateral information from the family of the patient may be useful in making these evaluations.

Patients who are intolerant of a particular medication can, of course, be switched to another agent or to another class of agents. For example, when TCA side effects prove intolerable, it may well be useful to switch to an SSRI. Within the SSRIs, adverse effects may not be seen when an alternative SSRI is used. When there is a poor response to medication, the first course of action is to optimise dose and duration of the treatment. Although dose-response relationship of the SSRIs has not been as well studied in the anxiety disorders as in depression, there appears to be a relatively flat dose-response curve.[7] Despite this, some patients may fail to respond to the standard initial starting dose, but do well at higher doses. Elderly patients generally require lower doses than younger adults. Particularly in the case of the TCAs, clinicians often prescribe suboptimal doses, rather than using doses of 150 mg or more of medications like imipramine.[70]

There is increasing awareness that some patients may be rapid metabolisers of antidepressant medication and, therefore, require significantly higher doses than usual.[71,72] Thus, for example, when patients on TCAs have little response and few anticholinergic

side effects on average doses of medication (eg, imipramine 150 mg), it may be useful to further increase dosage while monitoring ECG and perhaps drug levels. In addition, response to antidepressant medication may take six to eight weeks or even longer.

The dosage range for pregabalin is from 50-300 mg daily, with most patients requiring a minimum of 150 mg daily for therapeutic effect.

Buspirone treatment usually begins at 5 mg three times daily. This dose may be increased by 5 mg every two to three days. Therapeutic doses of buspirone range from 30 to 60 mg daily, typically given in divided doses. Buspirone has at least a two- to four-week time lag from initiation to clinical onset; optimum duration of a trial of treatment should thus be no less.

Although we have not included benzodiazepines as a first-line treatment, should these be used, it is important also to do this in an optimal fashion. In particular, it may be useful to replace short-acting agents with slow-release compounds or long-acting agents. All too frequently, patients on short-acting compounds have intermittent increases of anxiety before the next dose of medication is to be taken.

STEP 5: MAINTENANCE OF RESPONSE AND AUGMENTATION STRATEGIES FOR PARTIAL RESPONSE

At the end of a clinical trial of optimal dose and duration, patients should be thoroughly re-assessed. There is growing recognition of the importance of residual anxiety symptoms in causing disability and predicting relapse, and of the consequent necessity of aiming for remission of symptoms as the endpoint of treatment.[25]

When the patient has a good response to medication, it is important to reinforce the necessity for continuing the medication at the therapeutic dose despite this improvement.[47,52,73] Indeed, guidelines for maintenance therapy of GAD emphasise the safety of modern agents, the likelihood of additional episodes of illness in patients with repeated past episodes, and the theoretical possibility that appropriate treatment may prevent the onset of secondary disorders.[7,74,75] Such guidelines have become increasingly conservative, favouring longer courses of medication.[7,8,74]

Augmentation strategies in GAD have not been well researched. Augmentation offers the advantage of retaining any possible gains from the first agent, but the potential disadvantages of polypharmacy (more side effects and drug interactions).[76] Of all the augmentation strategies in the treatment of the anxiety disorders, however, arguably the most important is augmentation of pharmacotherapy with additional psychotherapy.[9,77,78] Pregabalin may be used to augment partial response to an SSRI or SNRI[49,79], and cautious augmentation of antidepressant drugs with atypical antipsychotics (risperidone, olanzapine, quetiapine) may be considered after specialist evaluation.[42,69]

STEP 6: FAILURE TO RESPOND

When GAD does not respond to a clinical trial of adequate dose and duration, it may be useful to re-assess a number of important factors that may influence the choice of further interventions:

a. **Comorbidity:** It is important to establish whether comorbid mood or other anxiety disorders are present. For example, comorbid dysthymia may not respond to buspirone alone, comorbid social anxiety disorder is unlikely to respond to a tricyclic antidepressant (other than clomipramine), and comorbid hypochondriasis may require high doses of serotonin re-uptake inhibitors. Excluding important comorbid psychiatric disorders is perhaps the most important step in the evaluation and management of refractory GAD.

b. **Adherence:** Many patients with GAD suffer from extreme anxiety and are in fact adherent with their medication. Nevertheless, there is perhaps a tendency for clinicians to overestimate patient adherence. Patients are particularly likely to be concerned about physical or psychological dependence on medication. It is well worth checking not only with the patient, but also with the family, whether medication is in fact taken as prescribed.

c. **Comorbid personality disorders:** Although antidepressants may be useful, additional interventions such as psychotherapy may be helpful in patients with chronic anxiety and comorbid personality disorder. While improvement in anxiety symptoms may reduce maladaptive behaviour in patients with

comorbid personality disorder, there are other patients (e.g., those with borderline personality disorder) in whom the personality disorder itself may need to be a major target of treatment.[31]

d. **Underlying medical disorder:** Patients with GAD who fail to show any noticeable response to treatment should be thoroughly re-assessed for the possibility of an underlying medical condition.[38] A range of different medical disorders may lead to chronic anxiety, including endocrine disorders (e.g., hyperthyroidism), respiratory disorders (e.g., chronic obstructive pulmonary disorder), cardiac disorders (e.g., congestive heart failure) and others.[80] If present, such disorders naturally require specific intervention. When using a benzodiazepine in patients with liver dysfunction, consider using those metabolised only by conjugation (e.g., lorazepam, oxazepam) so as to avoid accumulation.

e. **Pharmacokinetic issues:** Drug-drug interactions may result in a subtherapeutic dose of the prescribed antidepressant.

f. **Psychosocial issues:** In some cases, a diagnosis of an adjustment disorder with anxiety may be more accurate than that of GAD, and a psychotherapeutic approach may be indicated (this factor may partially explain high rates of placebo response in some clinical trials in GAD). In other cases of chronic anxiety, psychosocial factors may be enduring and therefore continuously complicate treatment of GAD until given independent attention.

STEP 7: TREATMENT RESISTANCE

Following failure of an adequate clinical trial of medication, and in the event of a thorough re-assessment providing no further important clues, the medication should be changed. The research literature on approaches to resistant GAD is unfortunately extremely scant[7] and specialist referral is recommended. Strategies include switching between drugs in the same class and across classes and high-dose prescribing of pregabalin (>200 mg per day).[79,81,82] Multiple trials of different medications may ultimately be required. Repetitive transcranial magnetic stimulation (rTMS) may also be efficacious and well-tolerated in generalised anxiety disorder.[83]

ADDITIONAL READING

1. Slee A, Nazareth I, Bondaronek P, *et al*. Pharmacological Treatments for Generalised Anxiety Disorder: A Systematic Review and Network Meta-Analysis. The Lancet. 2019 Feb 23;393(10173):768-77.
2. Baldwin DS, Anderson IM, Nutt DJ, *et al*. Evidence-based pharmacological treatment of anxiety disorders, posttraumatic stress disorder and obsessive-compulsive disorder: A revision of the 2005 guidelines from the British Association for Psychopharmacology. J Psychopharmacol. 2014;28(5):403-39.
3. Bandelow B, WFSBP Task Force on Mental Disorders in Primary Care, WFSBP Task Force on Anxiety Disorders, OCD and PTSD, *et al*. Guidelines for the pharmacological treatment of anxiety disorders, obsessive-compulsive disorder and posttraumatic stress disorder in primary care. International Journal of Psychiatry in Clinical Practice. 2012 Jun 1;16(2):77-84.
4. Davidson JR, Feltner DE, Dugar A. Management of generalized anxiety disorder in primary care: Identifying the challenges and unmet needs. Prim Care Companion J Clin Psychiatry. 2010;12(2):27451.
5. Sarris J, Moylan S, Camfield DA, *et al*. Complementary medicine, exercise, meditation, diet, and lifestyle modification for anxiety disorders: A review of current evidence. Evid Based Complement Alternat Med. 2012;2012:809653.
6. Katzman MA, Bleau P, Blier P, *et al*. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. BMC Psychiatry. 2014;14 Suppl 1:S1.
7. Andrews G, Bell C, Boyce P, *et al*. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of panic disorder, social anxiety disorder and generalised anxiety disorder. Aust N Z J Psychiatry. 2018 Dec; 52(12):1109-72.

REFERENCES

1. Davidson JR, Feltner DE, Dugar A. Management of generalized anxiety disorder in primary care: Identifying the challenges and unmet needs. Prim Care Companion J Clin Psychiatry. 2010;12(2).
2. Cuijpers P, Sijbrandij M, Koole S, *et al*. Psychological Treatment of Generalized Anxiety Disorder: A Meta-Analysis. Clin Psychol Rev. 2014;34(2):130-40.
3. Donker T, Griffiths KM, Cuijpers P, *et al*. Psychoeducation for Depression, Anxiety and Psychological Distress: A Meta-Analysis. BMC Med. 2009;7:79.

4. Parmentier H, Garcia-Campayo J, Prieto R. Comprehensive review of generalized anxiety disorder in primary care in Europe. Curr Med Res Opin. 2013;29(4):355-67.
5. Balon R. Rating scales for anxiety/anxiety disorders. Curr Psychiatry Rep. 2007;9(4):271-7.
6. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol. 1959;32(1):50-5.
7. Wittchen HU, Jacobi F, Rehm J, *et al*. The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur Neuropsychopharmacol. 2011;21(9):655-79.
8. Simon NM. Generalized anxiety disorder and psychiatric comorbidities such as depression, bipolar disorder, and substance abuse. J Clin Psychiatry. 2009;70 Suppl 2:10-4.
9. Beesdo K, Hoyer J, Jacobi F, *et al*. Association between generalized anxiety levels and pain in a community sample: Evidence for diagnostic specificity. J Anxiety Disord. 2009;23(5):684-93.
10. Brady KT, Haynes LF, Hartwell KJ, *et al*. Substance use disorders and anxiety: A treatment challenge for social workers. Soc Work Public Health. 2013;28(3-4):407-23.
11. Miloyan B, Byrne GJ, Pachana NA. Threshold and subthreshold generalized anxiety disorder in later life. Am J Geriatr Psychiatry. 2014.
12. Bland P. Tackling anxiety and depression in older people in primary care. Practitioner. 2012;256(1747):17-20, 2-3.
13. Gould RL, Coulson MC, Patel N, *et al*. Interventions for Reducing Benzodiazepine Use in Older People: Meta-Analysis of Randomised Controlled Trials. Br J Psychiatry. 2014;204(2):98-107.
14. Smith JP, Randall CL. Anxiety and alcohol use disorders: Comorbidity and treatment considerations. Alcohol Res. 2012;34(4):414-31.
15. Ipser JC, Wilson D, Akindipe TO, *et al*. Pharmacotherapy for anxiety and comorbid alcohol use disorders. Cochrane Database Syst Rev. 2015(1):CD007505.
16. Mackenzie CS, Reynolds K, Chou KL, *et al*. Prevalence and correlates of generalized anxiety disorder in a national sample of older adults. Am J Geriatr Psychiatry. 2011;19(4):305-15.
17. Latas M, Milovanovic S. Personality disorders and anxiety disorders: What is the relationship? Curr Opin Psychiatry. 2014;27(1):57-61.
18. Spinelli M. Antidepressant treatment during pregnancy. Am J Psychiatry. 2012;169(2):121-4.
19. Ellfolk M, Malm H. Risks associated with in utero and lactation exposure to selective serotonin re-uptake inhibitors (SSRIs). Reprod Toxicol. 2010;30(2):249-60.
20. Grigoriadis S, Vonderporten EH, Mamisashvili L, *et al*. Prenatal Exposure to Antidepressants and Persistent Pulmonary Hypertension of the Newborn: Systematic Review and Meta-Analysis. BMJ. 2014;348:f6932.
21. Okun ML, Ebert R, Saini B. A review of sleep-promoting medications used in pregnancy. Am J Obstet Gynecol. 2014.
22. Enato E, Moretti M, Koren G. The Fetal Safety of Benzodiazepines: An Updated Meta-Analysis. J Obstet Gynaecol Can. 2011;33(1):46-8.
23. Baldwin DS, Anderson IM, Nutt DJ, *et al*. Evidence-based pharmacological treatment of anxiety disorders, posttraumatic stress disorder and obsessive-compulsive disorder: A revision of the 2005 guidelines from the British Association for Psychopharmacology. J Psychopharmacol. 2014;28(5):403-39.
24. Bandelow B, Lichte T, Rudolf S, *et al*. The diagnosis of and treatment recommendations for anxiety disorders. Dtsch Arztebl Int. 2014;111(27-28): 473-80.
25. Zohar J, Westenberg HG. Anxiety disorders: A review of tricyclic antidepressants and selective serotonin re-uptake inhibitors. Acta Psychiatr Scand Suppl. 2000;403:39-49.
26. Kapczinski F, Lima MS, Souza JS, *et al*. Antidepressants for generalized anxiety disorder. Cochrane Database Syst Rev. 2003(2):CD003592.
27. Hidalgo RB, Tupler LA, Davidson JR. An effect-size analysis of pharmacologic treatments for generalized anxiety disorder. J Psychopharmacol. 2007;21(8):864-72.
28. Baldwin D, Woods R, Lawson R, *et al*. Efficacy of Drug Treatments for Generalised Anxiety Disorder: Systematic Review and Meta-Analysis. BMJ. 2011;342:d1199.
29. Carter NJ, McCormack PL. Duloxetine: A review of its use in the treatment of generalized anxiety disorder. CNS Drugs. 2009;23(6):523-41.
30. Stein DJ. Evidence-based treatment of anxiety disorders. Int J Psychiatry Clin Pract. 2006;10 Suppl 1:16-21.
31. Lydiard RB, Rickels K, Herman B, *et al*. Comparative efficacy of pregabalin and benzodiazepines in treating the psychic and somatic symptoms of generalized anxiety disorder. Int J Neuropsychopharmacol. 2010;13(2):229-41.
32. Boschen MJ. A Meta-Analysis of the Efficacy of Pregabalin in the Treatment of Generalized Anxiety Disorder. Can J Psychiatry. 2011;56(9):558-66.
33. Baldwin DS, Ajel K, Masdrakis VG, *et al*. Pregabalin for the treatment of generalized anxiety disorder: An update. Neuropsychiatr Dis Treat. 2013;9:883-92.
34. Pollack MH, Tiller J, Xie F, *et al*. Tiagabine in adult patients with generalized anxiety disorder: Results from 3 randomized, double-blind, placebo-controlled, parallel-group studies. J Clin Psychopharmacol. 2008;28(3):308-16.

35. Starcevic V. The reappraisal of benzodiazepines in the treatment of anxiety and related disorders. Expert Rev Neurother. 2014;14(11):1275-86.
36. Short- and Long-Term Use of Benzodiazepines in Patients with Generalized Anxiety Disorder: A Review of Guidelines. Ottawa ON: 2014 Canadian Agency for Drugs and Technologies in Health; 2014, Jul 28.
37. Huh J, Goebert D, Takeshita J, *et al*. Treatment of generalized anxiety disorder: A comprehensive review of the literature for psychopharmacologic alternatives to newer antidepressants and benzodiazepines. Prim Care Companion CNS Disord. 2011;13(2).
38. Guaiana G, Barbui C, Cipriani A. Hydroxyzine for generalised anxiety disorder. Cochrane Database Syst Rev. 2010(12):CD006815.
39. Zahreddine N, Richa S. Non-antidepressant treatment of generalized anxiety disorder. Curr Clin Pharmacol. 2013.
40. Sarris J, Moylan S, Camfield DA, *et al*. Complementary medicine, exercise, meditation, diet, and lifestyle modification for anxiety disorders: A review of current evidence. Evid Based Complement Alternat Med. 2012;2012:809653.
41. Lakhan SE, Vieira KF. Nutritional and Herbal Supplements for Anxiety and Anxiety-Related Disorders: Systematic Review. Nutr J. 2010;9:42.
42. LaLonde CD, Van Lieshout RJ. Treating Generalized Anxiety Disorder with Second Generation Antipsychotics: A Systematic Review and Meta-Analysis. J Clin Psychopharmacol. 2011;31(3):326-33.
43. Brown MN, Lapane KL, Luisi AF. The management of depression in older nursing home residents. J Am Geriatr Soc. 2002;50(1):69-76.
44. Niitsu T, Fabbri C, Bentini F, *et al*. Pharmacogenetics in Major Depression: A Comprehensive Meta-Analysis. Prog Neuropsychopharmacol Biol Psychiatry. 2013;45:183-94.
45. Gvozdic K, Brandl EJ, Taylor DL, *et al*. Genetics and personalized medicine in antidepressant treatment. Curr Pharm Des. 2012;18(36):5853-78.
46. Donovan MR, Glue P, Kolluri S, *et al*. Comparative Efficacy of Antidepressants in Preventing Relapse in Anxiety Disorders – a Meta-Analysis. J Affect Disord. 2010; 123(1-3):9-16.
47. Lam RW. Generalized anxiety disorder: How to treat, and for how long? Int J Psychiatry Clin Pract. 2006;10 Suppl 1:10-5.
48. Ballenger JC, Davidson JR, Lecrubier Y, *et al*. Consensus statement on generalized anxiety disorder from the International Consensus Group on Depression and Anxiety. J Clin Psychiatry. 2001;62 Suppl 11:53-8.
49. Fava M. Augmentation and combination strategies in treatment-resistant depression. J Clin Psychiatry. 2001;62 Suppl 18:4-11.
50. Bandelow B, Seidler-Brandler U, Becker A, *et al*. Meta-analysis of randomized controlled comparisons of psychopharmacological and psychological treatments for anxiety disorders. World J Biol Psychiatry. 2007;8(3):175-87.
51. Furukawa TA, Watanabe N, Churchill R. Combined psychotherapy plus antidepressants for panic disorder with or without agoraphobia. Cochrane Database Syst Rev. 2007(1):CD004364.
52. Simon NM, Otto MW, Worthington JJ, *et al*. Next-step strategies for panic disorder refractory to initial pharmacotherapy: A 3-phase randomized clinical trial. J Clin Psychiatry. 2009;70(11):1563-70.
53. Frampton JE. Pregabalin: A review of its use in adults with generalized anxiety disorder. CNS Drugs. 2014;28(9):835-54.
54. Hershenberg R, Gros DF, Brawman-Mintzer O. Role of atypical antipsychotics in the treatment of generalized anxiety disorder. CNS Drugs. 2014;28(6):519-33.
55. Bech P. Dose-response relationship of pregabalin in patients with generalized anxiety disorder. A pooled analysis of four placebo-controlled trials. Pharmacopsychiatry. 2007;40(4):163-8.

8: Obsessive-Compulsive and Related Disorders

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This chapter focuses on the pharmacotherapy of obsessive-compulsive disorder (OCD). Obsessive-compulsive disorder is, of course, characterised by obsessions and compulsions, and is one of a number of disorders that has been placed in a new chapter in DSM-5 and ICD-11 on "Obsessive-Compulsive and Related Disorders". These disorders are also characterised by repetitive thoughts or rituals, and may also respond to standard OCD treatment. In ICD-11, they include body dysmorphic disorder (characterised by recurrent concerns with imagined ugliness), olfactory reference disorder (characterised by the belief that one is emitting a foul odour), hypochondriasis (characterised by the preoccupation that one may have a severe illness), hoarding disorder (characterised by the accumulation of possessions) and body-focused repetitive behaviour disorders (BFRBs).[1] BFRBs include skin-picking disorder (characterised by recurrent skin-picking) and trichotillomania (characterised by recurrent hair-pulling).[1]

STEP 1: DIAGNOSIS OF OBSESSIVE-COMPULSIVE DISORDER

Current evidence indicates that OCD is not uncommon, and is often underdiagnosed and undertreated.[2,3] The converse possibility also exists that various disorders with intrusive

Table 8.1. Diagnostic guidelines for obsessive-compulsive disorder (adapted from ICD-11)

1. Presence of obsessions, compulsions, or both: **Obsessions as defined by A and B:** **A.** Recurrent and persistent thoughts (e.g., of contamination), impulses (e.g., to stab someone), or images (e.g., of violent scenes) that are experienced as intrusive and unwanted and are commonly associated with anxiety. **B.** The individual attempts to ignore or suppress such thoughts, urges or images, or to neutralise them with some other thought or action (i.e., by performing a compulsion). **Compulsions as defined by C and D:** **C.** Repetitive rituals, behaviours (e.g., hand-washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly. **D.** The behaviours or mental acts are aimed at preventing or reducing anxiety or distress, or preventing some dreaded event or situation; however, these behaviours or mental acts are not connected in a realistic way, or are clearly excessive.
2. The obsessions or compulsions are time-consuming (e.g., take more than one hour per day) or cause clinically significant distress or impairment in social, occupational or other important areas of functioning. If functioning is maintained, it is only through significant additional effort.
3. The obsessive-compulsive symptoms are not a manifestation of another medical condition, and are not attributed to the physiological effects of a substance (e.g., drug of abuse, a medication), including withdrawal effects.

symptoms, such as post-traumatic stress disorder or generalised anxiety disorder, can be misdiagnosed as OCD. Diagnostic guidelines for OCD are provided in Table 8.1.

Most patients with OCD have both obsessions (which often increase anxiety) and compulsions (behaviours or mental acts which often aim to decrease anxiety). Evaluation should include the assessment of symptom pattern, severity, and functional impairment. Some patients have poor or no insight (and so may be misdiagnosed with a psychotic disorder). Comorbid psychiatric disorders (including tic disorders), as well as comorbid medical conditions (including pregnancy), need to be accurately identified. There is growing evidence that OCD and/or tics in some patients, particularly children, are precipitated or exacerbated by streptococcal infections.[4]

Evaluation of the OCD patient also requires attention to psychosocial factors that may have precipitated or exacerbated OCD symptoms. For example, are family members involved in the patient's rituals? What is the patient's explanatory model of OCD – does he or she regard it as a sign of weakness or as evidence of brain dysfunction? Certainly, psycho-education as part of the management of OCD is crucial.[5] Similarly, cognitive-behavioural techniques are an important aspect of OCD treatment, whether used alone or in combination with medication.[6,7]

In this discussion, we assume that the patient is an adult. Nevertheless, there are increasing data on the pharmacotherapy of OCD in children.[8,9] Indeed, the algorithm here can readily be adapted for children, bearing in mind considerations such as differences in dosing and in risk-benefit determination (e.g., clinicians are less likely to use untested augmentation strategies in children). Specialist consultation may, however, be indicated in such cases, and cognisance should be taken of the possible increased risk of suicidal behaviour in adolescents using SSRIs.[9]

STEP 2: COMPLICATIONS IN DIAGNOSIS IMPACTING PHARMACOTHERAPY

Possible complications in OCD that may impact pharmacotherapy include the following:

a. **Severity:** Patients with severe symptoms may require brief hospitalisation to help contain symptoms.[10] In general, however, the principles of behaviour therapy suggest that patients should attempt to continue with their ordinary daily routines where possible.

b. **Melancholia:** Melancholic features of depression include loss of pleasure in activities, lack of reactivity to pleasurable stimuli, and various neurovegetative symptoms such as exacerbation of depression in the morning, early-morning awakening, and significant weight loss.[11] Patients with melancholia appear to respond better to antidepressants and electroconvulsive therapy and less favourably to psychotherapy and placebo than do non-melancholic patients.[12] There is some evidence that older drugs, such as tricyclic antidepressants (TCAs), may be more effective than selective serotonin re-uptake inhibitors (SSRIs) in patients with depression accompanied by melancholic features and hospitalised inpatients,[13,14] although not all evidence is consistent.[15] The only tricyclic that is effective in OCD is clomipramine.[16]

c. **Tourette's disorder:** This disorder is characterised by both motor and vocal tics. Many patients with TD have comorbid OCD, and DSM-5 recognises a subtype of OCD with tics. Although OCD in TD may respond to standard OCD treatments, additional medication that targets the tics (e.g., dopamine blockers such as haloperidol, pimozide, or risperidone and α2-agonists such as clonidine) may be necessary for resolution of the range of symptoms that characterise the disorder.[17]

d. **Pregnancy, lactation, menopause:** Pharmacotherapy should ideally be avoided during pregnancy and lactation. Nevertheless, where clinical considerations outweigh the risk of medication, such intervention should be considered after consultation with a specialist. Adverse-pregnancy-outcome studies can be difficult to interpret and it is not always clear whether outcomes observed are due to medications themselves or confounders such as the underlying mental illness.[18,19] SSRIs are generally considered safe first-line agents in pregnancy and there is currently no conclusive evidence of an association between treatment with these agents and increased risk for malformations, preterm birth, low birth weight or small-for- gestational-age births.[20] However, fluoxetine and paroxetine use in early pregnancy may be associated with a small increased risk for cardiovascular

malformations, and initiation of these agents should be avoided in the first trimester.[20,21] The risk of persistent pulmonary hypertension of the newborn has been shown to be increased for infants exposed to SSRIs in late pregnancy, although clinically the absolute risk is low.[22]

e. **Comorbid medical disorders and medications:** Clinicians need to be aware of the multiple interactions between medications used in the treatment of OCD and other medications, as well as the impact of a medication's adverse effects on medical disorders. Fortunately, certain SSRIs have relatively few interactions with other medications, and the SSRIs as a class are well tolerated in most medical disorders.

STEP 3: FIRST-LINE PHARMACOTHERAPY

The first line of medication in the treatment of OCD should comprise a serotonin re-uptake inhibitor (SRI) (see Figure 8.1.). Consistent with growing evidence for the importance of serotonin in OCD, both clomipramine and the SSRIs appear to be more effective than the noradrenergic re-uptake inhibitor, desipramine, and are first-line strategies in the treatment of OCD.[23-26] The efficacy and safety of clomipramine and the SSRIs in the treatment of OCD have been well researched.[27-29] The SRIs are also useful for body dysmorphic disorder, hypochondriasis, obsessive-compulsive symptoms in Tourette's disorder and in pathological skin-picking.[30-33]

In trichotillomania, there are limited data showing efficacy of clomipramine (a serotonergic tricyclic antidepressant), and N-acetylcysteine (a glutamate modulator) may be a useful first-line approach. N-acetylcysteine has also been shown useful in skin-picking.

Once a decision has been made to use an SRI, an immediate question is which to choose. Given the apparent lack of differences in efficacy between the SRIs,[29] the side-effect profile of these agents may be an important question in considering which agent to use first.[3] Certainly, there are invariably fewer side effects during treatment with the SSRIs than during treatment with clomipramine. Thus, it seems reasonable to suggest that treatment of OCD be initiated with a SSRI. While any SSRI is acceptable, the choice of SSRI may be influenced by characteristic side-effect profiles of the different SSRIs, and previous individual and familial responses to pharmacotherapy.

Continued on page 82

Figure 8.1. Algorithm for pharmacotherapy of OCD

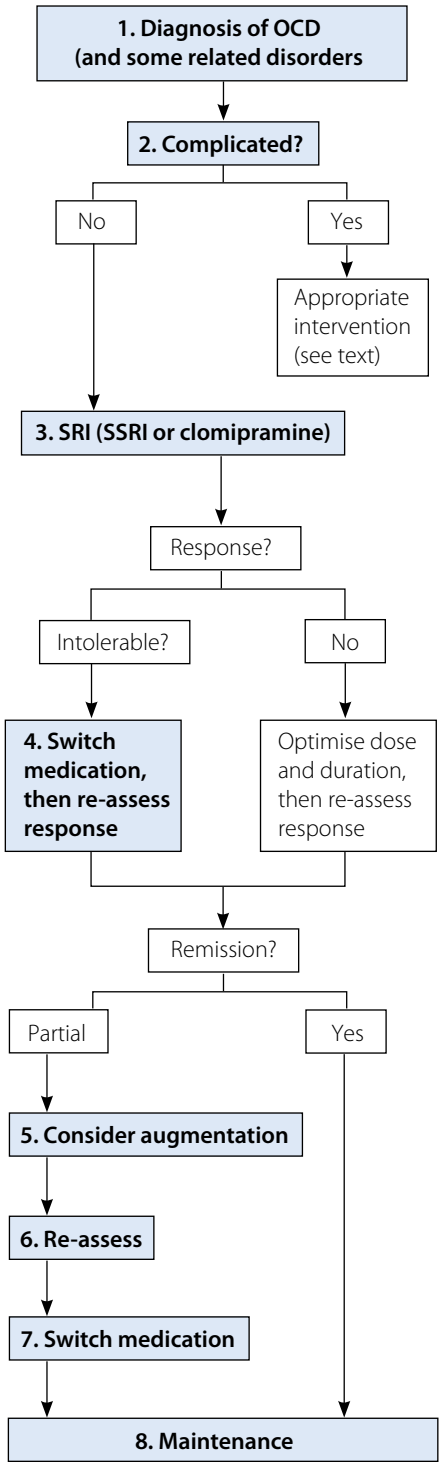

Table 8.2. Yale-Brown Obsessive-Compulsive Scale

"I am now going to ask several questions about your obsessive thoughts." (Make specific reference to the patient's target obsessions.)
1. TIME OCCUPIED BY OBSESSIVE THOUGHTS **Q:** How much of your time is occupied by obsessive thoughts? How frequently do the obsessive thoughts occur? 0 = None 1 = Mild, less than 1 hour/day or occasional intrusion 2 = Moderate, 1 to 3 hours/day or frequent intrusion 3 = Severe, greater than 3 and up to 8 hours/day or very frequent intrusion 4 = Extreme, greater than 8 hours/day or near constant intrusion
2. INTERFERENCE DUE TO OBSESSIVE THOUGHTS **Q:** How much do your obsessive thoughts interfere with your social or work (or role) functioning? Is there anything that you don't do because of them? 0 = None 1 = Mild, slight interference with social or occupational activities, but overall performance not impaired 2 = Moderate, definite interference with social or occupational performance, but still manageable 3 = Severe, causes substantial impairment in social or occupational performance 4 = Extreme, incapacitating
3. DISTRESS ASSOCIATED WITH OBSESSIVE THOUGHTS **Q:** How much distress do your obsessive thoughts cause you? 0 = None 1 = Mild, not too disturbing 2 = Moderate, disturbing, but still manageable 3 = Severe, very disturbing 4 = Extreme, near constant and disabling distress
4. RESISTANCE AGAINST OBSESSIONS **Q:** How much of an effort do you make to resist the obsessive thoughts? How often do you try to disregard or turn your attention away from these thoughts as they enter your mind? 0 = Makes an effort to always resist, or symptoms so minimal doesn't need to actively resist 1 = Tries to resist most of the time 2 = Makes some effort to resist 3 = Yields to all obsessions without attempting to control them, but does so with some reluctance 4 = Completely and willingly yields to all obsessions
5. DEGREE OF CONTROL OVER OBSESSIVE THOUGHTS **Q:** How much control do you have over your obsessive thoughts? How successful are you in stopping or diverting your obsessive thinking? Can you dismiss them? 0 = Complete control 1 = Much control, usually able to stop or divert obsessions with some effort and concentration 2 = Moderate control, sometimes able to stop or divert obsessions 3 = Little control, rarely successful in stopping or dismissing obsessions, can only divert attention with difficulty 4 = No control, experienced as completely involuntary, rarely able to even momentarily alter obsessive thinking

Table 8.2. (continued)

"The next several questions are about your compulsive behaviours." (Make specific reference to the patient's target compulsions.)
6. TIME SPENT PERFORMING COMPULSIVE BEHAVIOURS **Q:** How much time do you spend performing compulsive behaviours? How much longer than most people does it take to complete routine activities because of your rituals? How frequently do you perform compulsions? 0 = None 1 = Mild (spends less than 1 hour/day performing compulsions), or occasional performance of compulsive behaviours 2 = Moderate (spends from 1 to 3 hours/day performing compulsions), or frequent performance of compulsive behaviours 3 = Severe (spends more than 3 and up to 8 hours/day performing compulsions), or very frequent performance of compulsive behaviours 4 = Extreme (spends more than 8 hours/day performing compulsions), or near constant performance of compulsive behaviours (too numerous to count)
7. INTERFERENCE DUE TO COMPULSIVE BEHAVIOURS **Q:** How much do your compulsive behaviours interfere with your social or work (or role) functioning? Is there anything that you don't do because of the compulsions? 0 = None 1 = Mild, slight interference with social or occupational activities, but overall performance not impaired 2 = Moderate, definite interference with social or occupational performance, but still manageable 3 = Severe, causes substantial impairment in social or occupational performance 4 = Extreme, incapacitating
8. DISTRESS ASSOCIATED WITH COMPULSIVE BEHAVIOUR **Q:** How would you feel if prevented from performing your compulsion(s)? How anxious would you become? How anxious do you get while performing compulsions until you are satisfied they are completed? 0 = None 1 = Mild, only slightly anxious if compulsions prevented, or only slight anxiety during performance of compulsions 2 = Moderate, reports that anxiety would mount, but remain manageable if compulsions prevented, or that anxiety increases, but remains manageable during performance of compulsions 3 = Severe, prominent and very disturbing increase in anxiety if compulsions interrupted, or prominent and very disturbing increase in anxiety during performance of compulsions 4 = Extreme, incapacitating anxiety from any intervention aimed at modifying activity, or incapacitating anxiety develops during performance of compulsions
9. RESISTANCE AGAINST COMPULSIONS **Q:** How much of an effort do you make to resist the compulsions? 0 = Makes an effort to always resist, or symptoms so minimal doesn't need to actively resist 1 = Tries to resist most of the time 2 = Makes some effort to resist 3 = Yields to almost all compulsions without attempting to control them, but does so with some reluctance 4 = Completely and willingly yields to all compulsions
10. DEGREE OF CONTROL OVER COMPULSIVE BEHAVIOUR **Q:** How strong is the drive to perform the compulsive behaviour? How much control do you have over the compulsions? 0 = Complete control 1 = Much control, experiences pressure to perform the behaviour, but usually able to exercise voluntary control over it 2 = Moderate control, strong pressure to perform behaviour, can control it only with difficulty 3 = Little control, very strong drive to perform behaviour, must be carried to completion, can only delay with difficulty 4 = No control, drive to perform behaviour experienced as completely involuntary and overpowering, rarely able to delay activity even momentarily

Low doses should initially be used in patients with comorbid panic disorder.

STEP 4: ASSESS RESPONSE TO TREATMENT

To determine response to medication, it is important to ask about change in those symptoms initially targeted for treatment. Side effects of the medication should also be determined, with particular attention to those that patients may be reluctant to disclose (e.g., sexual dysfunction). It may be useful to complete a symptom-rating scale (see Table 8.2.) to help quantify response to medication.[34]

Patients who are intolerant of a particular medication can, of course, be switched to another agent. Within the SRIs, adverse effects may not be seen when an alternative SSRI is used.

When there is a poor response to medication, it is important to optimise dosage and duration of the medication. Although some patients with OCD respond to standard doses of SRIs, others require doses that are much higher than in depression.[35] In adults, clomipramine should be increased to approximately 250 mg, and the SSRIs should be increased to maximal dosages (e.g., 60 to 80 mg of fluoxetine). Unfortunately, the likelihood of side effects also increases at these doses. Electrocardiogram monitoring may be necessary when children and adolescents, or patients with pre-existing heart disease, are treated with clomipramine. Also, citalopram has a black box warning at doses higher than 40 mg per day.

Furthermore, response to SSRIs in OCD may take rather longer than in many other disorders – up to 12 weeks.[24,27] It is important to give each patient a trial of medication that is of adequate duration. Patients therefore need to be educated that response may take a significant length of time and that they need to remain optimistic even when no change is seen at first.

STEP 5: MAINTENANCE OF RESPONSE AND AUGMENTATION STRATEGIES FOR PARTIAL RESPONSE

At the end of a clinical trial of optimal dose and duration, patients should be thoroughly re-assessed. There is growing recognition of the importance of residual anxiety symptoms in causing disability and predicting relapse, and of the consequent necessity of aiming for remission of symptoms as the endpoint of treatment.[3,24,25,36] Nevertheless, many OCD patients who are judged "responders" to medication therapy may continue to experience obsessions and compulsions, albeit with less intensity. In clinical trials, a decrease of 25-35% on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) typically corresponds to a categorical treatment response.[37]

In patients where an SRI is effective, maintenance pharmacotherapy should be instituted. Rapid discontinuation of these agents risks the return of symptoms. Nevertheless, a maintenance dose of SSRIs in OCD may be lower than the dose initially required during acute treatment.[38] Treatment guidelines recommend a duration of 12-24 months, before gradual tapering of the dose.[24,25,39] Concomitant behavioural treatment during pharmacotherapy may well increase the chance of being able to discontinue medication without relapse.[6]

Comparison of augmentation with switching strategies in OCD has not been well researched. Augmentation offers the advantage of retaining any possible gains from the first agent, but the potential disadvantages of polypharmacy (more side effects, drug interactions).[40,41] Of all the augmentation strategies in the treatment of OCD, perhaps the most important is augmentation of pharmacotherapy with additional psychotherapy; this is more efficacious than pharmacological augmentation with an atypical antipsychotic.[7,42] However, when there is a partial response despite an optimum trial of medication, or when there are comorbid tics, it may be useful to consider an augmenting medication. Certainly, in patients with comorbid tics, there is good evidence that augmentation of a SRI with a dopamine blocker can be effective.[43] The introduction of the second-generation antipsychotics has led to increased use of these agents in the augmentation therapy of OCD, and they appear useful for treatment-refractory patients even in the absence of comorbid tics.[44,45] Another possible strategy is to supplement an SSRI with a low dose of clomipramine,[46] although careful monitoring of adverse effects and electrocardiographs may be warranted with such a combination. There is increasing attention to glutamatergic augmentation, with a number of RTCs indicating the efficacy of memantine.[47,48] A range of other augmentation strategies has been suggested, but there are few positive controlled trials. There is also relatively little work on augmentation strategies

in OCD-related disorders, although addition of a dopamine blocker, or N-acetylcysteine may also be useful in some of these patients.[49-51]

STEP 6: FAILURE TO RESPOND

When OCD does not respond to a clinical trial of optimal dose and duration, it is useful to re-assess a number of factors. The presence of certain features may impact on the choice of the subsequent intervention.

a. **Adherence:** Clinicians often over-estimate the adherence of their patients and it is often useful to check with patients and their families whether medication is being taken as prescribed. Many patients worry that medication is addictive or a "crutch".
b. **Comorbid substance use:** In the presence of active alcohol or substance use, it may be necessary to shift the emphasis of treatment towards a substance-use disorder as the primary diagnosis, with the anxiety as a secondary problem. Detoxification may be a necessary first step in the management of these patients.[52,53]
c. **Comorbid personality disorders:** Although SSRIs may be useful, additional interventions such as psychotherapy may be crucial in patients with OCD and comorbid personality disorder. While improvement in OCD symptoms may reduce maladaptive behaviour in comorbid personality disorder, the personality disorder itself may need to be a major target of treatment.
d. **Underlying medical disorder:** Anxious patients who fail to respond to medication should be thoroughly re-assessed for an underlying medical disorder. In OCD in children, the role of streptococcal throat infection may be particularly important.[4] Antibiotics could then be a consideration.[54]
e. **Pharmacokinetic issues:** Drug-drug interactions may result in a sub-therapeutic dose of the prescribed antidepressant.
f. **Psychosocial issues:** Psychosocial circumstances that continue to complicate the course of OCD need to be assessed, as these may necessitate appropriate intervention. In particular, the participation of friends and family in rituals may serve to derail treatment.

STEP 7: TREATMENT RESISTANCE

After the failure of an adequate clinical trial of medication in a patient where re-assessment sheds no light on any further unresolved factors, a different agent should be used.[55] Although an SRI has less chance of being effective in patients who have already failed a number of trials of other SRIs, some of these patients will, in fact, ultimately respond to a new SRI.[28] Given the possible superiority of clomipramine in certain cases of OCD and depression, it may be argued that all OCD patients who have failed to respond to one or more of the SSRIs deserve a trial of clomipramine.[56] While results of studies correlating plasma drug levels and therapeutic response in OCD have been mixed, in the case of clomipramine, obtaining drug levels at high doses may be useful.[57]

Some evidence suggests that certain non-SRI agents, such as venlafaxine, duloxetine, mirtazapine and agomelatine, may on occasion be effective in treatment-resistant OCD, but there is a need for more rigorous study.[58,59] Reviews of intravenous clomipramine also show efficacy in treatment-resistant OCD.[60] Drugs that are known to modulate glutamatergic function have been suggested to be efficacious in the augmentation of partial response to SRIs in OCD – such agents include N-acetylcysteine, topiramate, riluzole and memantine – with memantine having the largest evidence base currently.[47,48,50,61-64]

Deep transcranial magnetic stimulation is now FDA-approved for OCD, and may also be considered in treatment-refractory patients. In the pivotal trial showing efficacy of TMS, this modality is combined with CBT.[65,66]

For patients who have failed multiple medication and behavioural treatments (including intensive partial or full hospitalisation programmes[67]), and where severity of the disorder is marked, neurosurgery may also be considered.[68] Several studies have suggested that specific lesions to the cortico-striatal pathways, or the use of deep-brain stimulation, may lead to significant reduction in OCD symptoms in treatment-refractory patients.[3] A review of case reports and case series have shown electroconvulsive therapy may be helpful for some OCD patients, however there are no randomised, controlled trials.[69]

ADDITIONAL READING

1. Baldwin DS, Anderson IM, Nutt DJ, *et al.* Evidence-based pharmacological treatment of anxiety disorders, posttraumatic stress disorder and obsessive-compulsive disorder: A revision of the 2005 guidelines from the British Association for Psychopharmacology. J Psychopharmacol. 2014;28(5):403-39.
2. Koran LM, Hanna GL, Hollander E, *et al.* Practice guideline for the treatment of patients with

obsessive- compulsive disorder. Am J Psychiatry. 2007;164(7 Suppl):5-53.
3. Bandelow B, Sher L, Bunevicius R, *et al.* Guidelines for the pharmacological treatment of anxiety disorders, obsessive-compulsive disorder and posttraumatic stress disorder in primary care. Int J Psychiatry Clin Pract. 2012;16(2):77-84.
4. Fineberg NA, Hollander E, Pallanti S, *et al.* Clinical advances in obsessive-compulsive disorder: A position statement by the International College of Obsessive-Compulsive Spectrum Disorders. Int Clin Psychopharmacol. 2020 Jul;35(4):173-93.
5. Katzman MA, Bleau P, Blier P, *et al.* Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. BMC Psychiatry. 2014; 14 Suppl 1:S1.
6. Hoffman J, Stein DJ. Psychopharmacotherapy of obsessive-compulsive and related disorders. NeuroPsychopharmacotherapy. 2021:1-20.
7. Abramowitz JS, Jacoby RJ. Obsessive- compulsive and related disorders: A critical review of the new diagnostic class. Annu Rev Clin Psychol. 2015.

REFERENCES

1. World Health Organization. International Classification of Diseases for Mortality and Morbidity Statistics (11th Revision). Geneva: World Health Organization; 2018.
2. Ruscio AM, Stein DJ, Chiu WT, *et al.* The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. Mol Psychiatry. 2010 Jan;15(1):53-63.
3. Fineberg NA, Hollander E, Pallanti S, *et al.* Clinical advances in obsessive-compulsive disorder: A position statement by the International College of Obsessive-Compulsive Spectrum Disorders. Int Clin Psychopharmacol. 2020 Jul;35(4):173-93.
4. Williams KA, Swedo SE. Post-infectious autoimmune disorders: Sydenham's chorea, PANDAS and beyond. Brain Res. 2015 Aug 18;1617:144-54.
5. Donker T, Griffiths KM, Cuijpers P, *et al.* Psychoeducation for Depression, Anxiety and Psychological Distress: A Meta-Analysis. BMC Med. 2009;7:79.
6. McKay D, Sookman D, Neziroglu F, *et al.* Efficacy of cognitive-behavioral therapy for obsessive-compulsive disorder. Psychiatry Res. 2015;225(3):236-46.
7. Olatunji BO, Davis ML, Powers MB, *et al.* Cognitive-Behavioral Therapy for Obsessive-Compulsive Disorder: A Meta-Analysis of Treatment Outcome and Moderators. J Psychiatr Res. 2013;47(1):33-41.
8. Öst L-G, Riise EN, Wergeland GJ, *et al.* Cognitive Behavioral and Pharmacological Treatments of OCD in Children: A Systematic Review and Meta-Analysis. J Anxiety Disord. 2016 Oct;43:58-69.
9. Ipser JC, Stein DJ, Hawkridge S, *et al.* Pharmacotherapy for anxiety disorders in children and adolescents. Cochrane Database Syst Rev. 2009(3):CD005170.
10. Stewart SE, Stack DE, Farrell C, *et al.* Effectiveness of intensive residential treatment (IRT) for severe, refractory obsessive-compulsive disorder. J Psychiatr Res. 2005;39(6):603-9.
11. Fink M, Taylor MA. Resurrecting melancholia. Acta Psychiatr Scand Suppl. 2007(433):14-20.
12. Brown WA. Treatment response in melancholia. Acta Psychiatr Scand Suppl. 2007(433):125-9.
13. Anderson IM. SSRIS versus Tricyclic Antidepressants in Depressed Inpatients: A Meta-Analysis of Efficacy and Tolerability. Depress Anxiety. 1998;7(Suppl 1):11-7.
14. Perry PJ. Pharmacotherapy for major depression with melancholic features: Relative efficacy of tricyclic versus selective serotonin re-uptake inhibitor antidepressants. J Affect Disord. 1996;39(1):1-6.
15. Sneed JR, Reinlieb ME, Rutherford BR, *et al.* Antidepressant treatment of melancholia in older adults. Am J Geriatr Psychiatry. 2014 Jan; 22(1):46-52.
16. Montgomery SA. Clomipramine in obsessional neurosis: A placebo-controlled trial. Pharm Med. 1980;1:189-92.
17. Waldon K, Hill J, Termine C, *et al.* Trials of Pharmacological Interventions for Tourette Syndrome: A Systematic Review. Behav Neurol. 2013;26(4):265-73.
18. Spinelli M. Antidepressant treatment during pregnancy. Am J Psychiatry. 2012;169(2):121-4.
19. Fischer Fumeaux CJ, Morisod Harari M, Weisskopf E, *et al.* Risk-benefit balance assessment of SSRI antidepressant use during pregnancy and lactation based on best available evidence – an update. Expert Opin Drug Saf. 2019 Oct;18(10):949-63.
20. Ellfolk M, Malm H. Risks associated with in utero and lactation exposure to selective serotonin re-uptake inhibitors (SSRIs). Reprod Toxicol. 2010;30(2):249-60.
21. Zhang T-N, Gao S-Y, Shen Z-Q, *et al.* Use of Selective Serotonin-Re-uptake Inhibitors in the First Trimester and Risk of Cardiovascular-Related Malformations: A Meta-Analysis of Cohort Studies. Sci Rep. 2017 Feb 21;7:43085.
22. Grigoriadis S, Vonderporten EH, Mamisashvili L, *et al.* Prenatal Exposure to Antidepressants and Persistent Pulmonary Hypertension of the Newborn: Systematic Review and Meta-Analysis. BMJ. 2014;348:f6932.

23. Pittenger C, Bloch MH. Pharmacological treatment of obsessive-compulsive disorder. Psychiatr Clin North Am. 2014;37(3):375-91.
24. Baldwin DS, Anderson IM, Nutt DJ, *et al.* Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: A revision of the 2005 guidelines from the British Association for Psychopharmacology. J Psychopharmacol Oxf Engl. 2014 May;28(5):403-39.
25. Bandelow B, Sher L, Bunevicius R, *et al.* Guidelines for the pharmacological treatment of anxiety disorders, obsessive-compulsive disorder and post-traumatic stress disorder in primary care. Int J Psychiatry Clin Pr. 2012;16(2):77-84.
26. Katzman MA, Bleau P, Blier P, *et al.* Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. BMC Psychiatry. 2014;14 Suppl 1:S1.
27. Fineberg NA, Reghunandanan S, Brown A, *et al.* Pharmacotherapy of obsessive-compulsive disorder: Evidence-based treatment and beyond. Aust N Z J Psychiatry. 2013;47(2):121-41.
28. Soomro GM, Altman D, Rajagopal S, *et al.* Selective serotonin re-uptake inhibitors (SSRIs) versus placebo for obsessive compulsive disorder (OCD). Cochrane Database Syst Rev. 2008;(1):CD001765.
29. Skapinakis P, Caldwell DM, Hollingworth W, *et al.* Pharmacological and psychotherapeutic Interventions for Management of Obsessive-Compulsive Disorder in Adults: A Systematic Review and Network Meta-Analysis. Lancet Psychiatry. 2016 Aug;3(8):730-9.
30. Phillips KA, Pagano ME, Menard W. Pharmacotherapy for body dysmorphic disorder: Treatment received and illness severity. Ann Clin Psychiatry. 2006;18(4):251-7.
31. Louw K-A, Hoare J, Stein DJ. Pharmacological treatments for hypochondriasis: A review. Curr Psychiatry Rev. 2014;10(1):70-4.
32. Jafferany M, Patel A. Skin-picking disorder: A guide to diagnosis and management. CNS Drugs. 2019 Apr;33(4):337-46.
33. Hoffman J, Williams T, Rothbart R, *et al.* Pharmacotherapy for trichotillomania. Cochrane Database Syst Rev. 2021(9):CD007662.
34. Goodman WK, Price LH, Rasmussen SA, *et al.* The Yale-Brown Obsessive Compulsive Scale: I. Development, use, and reliability. Arch Gen Psychiatry. 1989;46(11):1006-11.
35. Bloch MH, McGuire J, Landeros-Weisenberger A, *et al.* Meta-Analysis of the Dose-Response Relationship of SSRI in Obsessive-Compulsive Disorder. Mol Psychiatry. 2010;15(8):850-5.
36. Janardhan Reddy YC, Sundar AS, Narayanaswamy JC, *et al.* Clinical practice guidelines for obsessive-compulsive disorder. Indian J Psychiatry. 2017 Jan;59(Suppl 1):S74-90.
37. Tolin DF, Abramowitz JS, Diefenbach GJ. Defining response in clinical trials for obsessive-compulsive disorder: A signal detection analysis of the Yale-Brown obsessive compulsive scale. J Clin Psychiatry. 2005;66(12):1549-57.
38. Pato MT, Hill JL, Murphy DL. A clomipramine dosage reduction study in the course of long-term treatment of obsessive-compulsive disorder patients. Psychopharmacol Bull. 1990;26(2):211-4.
39. Koran LM, Hanna GL, Hollander E, *et al.* Practice guideline for the treatment of patients with obsessive-compulsive disorder. Am J Psychiatry. 2007;164(7):5-53.
40. Skapinakis P, Papatheodorou T, Mavreas V. Antipsychotic Augmentation of Serotonergic Antidepressants in Treatment-Resistant Obsessive-Compulsive Disorder: A Meta-Analysis of the Randomized Controlled Trials. Eur Neuropsychopharmacol. 2007;17(2):79-93.
41. Papakostas GI, Shelton RC, Smith J, *et al.* Augmentation of Antidepressants with Atypical Antipsychotic Medications for Treatment-Resistant Major Depressive Disorder: A Meta-Analysis. J Clin Psychiatry. 2007;68(6):826-31.
42. Simpson HB, Foa EB, Liebowitz MR, *et al.* Cognitive-Behavioral Therapy vs Risperidone for Augmenting Serotonin Re-uptake Inhibitors in Obsessive-Compulsive Disorder: A Randomized Clinical Trial. JAMA Psychiatry. 2013 Nov; 70(11):1190-9.
43. Van Ameringen M, Simpson W, Patterson B, *et al.* Pharmacological treatment strategies in obsessive compulsive disorder: A cross-sectional view in nine international OCD centers. J Psychopharmacol (Oxf). 2014 Jun 1;28(6): 596-602.
44. Veale D, Miles S, Smallcombe N, *et al.* Atypical Antipsychotic Augmentation in SSRI Treatment Refractory Obsessive-Compulsive Disorder: A Systematic Review and Meta-Analysis. BMC Psychiatry. 2014;14(1):317.
45. Komossa K, Depping AM, Meyer M, *et al.* Second-generation antipsychotics for obsessive compulsive disorder. Cochrane Database Syst Rev. 2010(12):CD008141.
46. Andrade C. Augmenting selective serotonin re-uptake inhibitors with clomipramine in obsessive-compulsive disorder: Benefits and risks. J Clin Psychiatry. 2013;74(12):e1128-33.
47. Kishi T, Matsuda Y, Iwata N. Combination Therapy of Serotonin Re-uptake Inhibitors and

Memantine for Obsessive- Compulsive Disorder: A Meta-Analysis of Double-Blind, Randomized, Placebo-Controlled Trials. J Alzheimers Dis JAD. 2018;64(1):43-8.
48. Modarresi A, Chaibakhsh S, Koulaeinejad N, *et al.* A Systematic Review and Meta-Analysis: Memantine Augmentation in Moderate to Severe Obsessive-Compulsive Disorder. Psychiatry Res. 2019 Dec;282:112602.
49. Lochner C, Stein DJ. Treatment of Obsessive-Compulsive and Related Disorders. Curr Treat Options Psychiatry. 2014 Sep 1;1(3):225-34.
50. Gadallah A-HA, Ebada MA, Gadallah A, *et al.* Efficacy and Safety of N-Acetylcysteine as Add-On Therapy in the Treatment of Obsessive-Compulsive Disorder: A Systematic Review and Meta-Analysis. J Obsessive-Compuls Relat Disord. 2020 Apr 1;25:100529.
51. Mataix-Cols D, Fernández de la Cruz L, Monzani B, *et al.* D-Cycloserine Augmentation of Exposure-Based Cognitive Behavior Therapy for Anxiety, Obsessive-Compulsive, and Posttraumatic Stress Disorders: A Systematic Review and Meta-Analysis of Individual Participant Data. JAMA Psychiatry. 2017 May 1;74(5):501-10.
52. Smith JP, Randall CL. Anxiety and alcohol use disorders: Comorbidity and treatment considerations. Alcohol Res. 2012;34(4):414-31.
53. Hobbs JD, Kushner MG, Lee SS, *et al.* Meta-analysis of supplemental treatment for depressive and anxiety disorders in patients being treated for alcohol dependence. Am J Addict. 2011;20(4):319-29.
54. Burchi E, Pallanti S. Antibiotics for PANDAS? Limited evidence: Review and putative mechanisms of action. Prim Care Companion CNS Disord. 2018 May 3;20(3):17r02232.
55. Albert U, Marazziti D, Di Salvo G, *et al.* A systematic review of evidence-based treatment strategies for obsessive-compulsive disorder resistant to first-line pharmacotherapy. Curr Med Chem. 2018;25(41):5647-61.
56. Kaplan A, Hollander E. A review of pharmacologic treatments for obsessive-compulsive disorder. Psychiatr Serv. 2003;54(8):1111-8.
57. Marazziti D, Baroni S, Faravelli L, *et al.* Plasma clomipramine levels in adult patients with obsessive-compulsive disorder. Int Clin Psychopharmacol. 2012;27(1):55–60.
58. Del Casale A, Sorice S, Padovano A, *et al.* Psychopharmacological treatment of obsessive-compulsive disorder (OCD). Curr Neuropharmacol. 2019;17(8):710-36.
59. Pizarro M, Fontenelle LF, Paravidino DC, *et al.* An updated review of antidepressants with marked serotonergic effects in obsessive-compulsive disorder. Expert Opin Pharmacother. 2014 Jul;15(10):1391-401.
60. Ravindran LN, Jung SM, Ravindran AV. Intravenous anti-obsessive agents: A review. J Psychopharmacol. 2010;24(3):287-96.
61. Dean O, Giorlando F, Berk M. N-acetylcysteine in psychiatry: Current therapeutic evidence and potential mechanisms of action. J Psychiatry Neurosci JPN. 2011 Mar;36(2):78-86.
62. Pittenger C. Glutamatergic agents for OCD and related disorders. Curr Treat Options Psychiatry. 2015 Sep;2(3):271-83.
63. Abdel-Ahad P, Kazour F. Non-antidepressant pharmacological treatment of obsessive compulsive disorder: A comprehensive review Curr Clin Pharmacol. 2013;
64. Marinova Z, Chuang D-M, Fineberg N. Glutamate-modulating drugs as a potential therapeutic strategy in obsessive-compulsive disorder. Curr Neuropharmacol. 2017;15(7):977-95.
65. Roth Y, Barnea-Ygael N, Carmi L, *et al.* Deep transcranial magnetic stimulation for obsessive-compulsive disorder is efficacious even in patients who failed multiple medications and CBT. Psychiatry Res. 2020 Aug;290:113179.
66. Acevedo N, Bosanac P, Pikoos T, *et al.* Therapeutic Neurostimulation in Obsessive-Compulsive and Related Disorders: A Systematic Review. Brain Sci. 2021 Jul 19;11(7):948.
67. Boschen MJ, Drummond LM, Pillay A, *et al.* Predicting outcome of treatment for severe, treatment resistant OCD in inpatient and community settings. J Behav Ther Exp Psychiatry. 2010;41(2):90-5.
68. Hamani C, Pilitsis J, Rughani AI, *et al.* Deep Brain Stimulation for Obsessive-Compulsive Disorder: Systematic Review and Evidence-Based Guideline sponsored by the American Society for Stereotactic and Functional Neurosurgery and the Congress of Neurological Surgeons (CNS) and endorsed by the CNS and American Association of Neurological Surgeons. Neurosurgery. 2014 Oct;75(4):327-33.
69. Dos Santos-Ribeiro S, de Salles Andrade JB, Quintas JN, *et al.* A Systematic Review of the Utility of Electroconvulsive Therapy in Broadly Defined Obsessive-Compulsive-Related Disorders. Prim Care Companion CNS Disord. 2018 Oct 18;20(5):24760.

9: Post-Traumatic Stress Disorder

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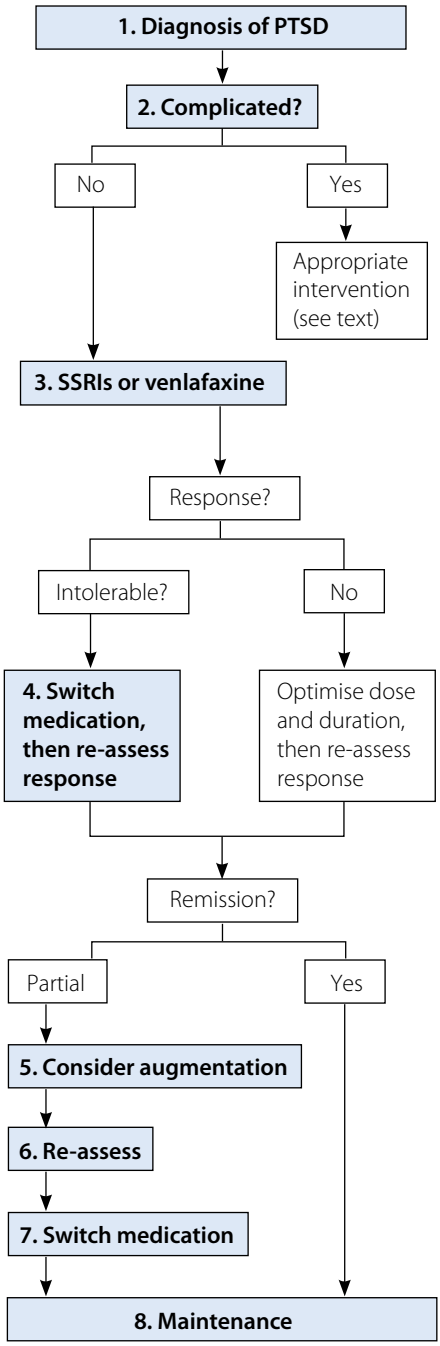
Post-traumatic stress disorder (PTSD) is a prevalent and disabling psychiatric disorder.[1-3] PTSD is characterised by exposure to trauma followed by re-experiencing, avoidance, negative alterations in cognition and mood, and hyperarousal symptoms associated with the traumatic event.[4,5] The symptoms of PTSD may be misdiagnosed as physical illness in primary care settings. PTSD is associated with considerable comorbidity with anxiety disorders, depression and substance-use disorders.[6] In addition, PTSD may be associated with significant morbidity and functional impairment.[3]

The role of psychotherapy in the treatment of PTSD must be emphasised.[7-9] Debriefing sessions focussed on the traumatic event are no longer recommended for routine practice,[10] and routine, multiple session interventions for everyone exposed to traumatic events also lacks evidence of benefit.[11] However, trauma-focused cognitive behaviour therapy (TF-CBT) is effective in patients with acute traumatic stress symptoms[12], and TF-CBT provided within three to six months of the traumatic event may help prevent chronic PTSD symptoms.[11] In the presence of chronic PTSD symptoms (longer than three months) TF-CBT and eye movement desensitisation and reprocessing (EMDR) may reduce the severity of PTSD symptoms.[7,13] In

Figure 9.1. Algorithm for pharmacotherapy of post-traumatic stress disorder (PTSD)



addition, psycho-education of both patient and family is crucial in the treatment of PTSD.[14] There is currently insufficient evidence to support or refute the combined use of psychotherapy and pharmacotherapy in the treatment of PTSD.[6,15,16] In resource-limited settings, treatments should arguably be offered in a stepwise fashion, though little guidance is currently available regarding the optimal sequencing of interventions and they may need to be assessed on a case-by-case basis.[6,15] It is reasonable to consider combining psychotherapy and pharmacotherapy if either treatment has been unsuccessful or partially successful on its own.[17,18]

The algorithm (see Figure 9.1.) assumes that the patient is an adult. Although there are fewer data on the treatment of children and adolescents with PTSD, what does exist suggests that selective serotonin re-uptake inhibitors (SSRIs) should be considered as first-line pharmacological agents, although cognisance should be taken of the black box warning of possible increased suicidal behaviour issued by the FDA in this regard.[19] Specialist consultation may be indicated in children and adolescents.

STEP 1: DIAGNOSIS OF PTSD

The first step in any treatment algorithm involves correct diagnosis. The diagnosis of PTSD begins with establishing a history of trauma. The definition of a traumatic event has been refined in ICD-11 and includes exposure to actual or threatened death, serious injury or sexual violence in one of the following ways: directly experiencing an event, witnessing the event as it occurred to others, learning that the event has occurred to a close friend or relative and repeated or extreme exposure to aversive details of the traumatic event (e.g., police officers repeatedly exposed to details of child abuse[5] [see Table 9.1.]). It is important to note that the majority of individuals have experienced some form of trauma, that many experience some symptoms after such trauma, but that only a minority of people develop persistent symptoms of PTSD.[20] Several risk factors, such as trauma severity, lack of social support, sex, and additional life stress, have been associated with the development of PTSD.[21]

In individuals who develop PTSD, the traumatic event is followed by symptoms of re-experiencing, avoidance, negative alterations in cognition and mood, and hyperarousal, that are present for at least several weeks and lead to impairment in personal, family, social, educational, occupational or other areas of functioning (see Table 9.1.). Panic attacks (see Table 9.2.) may occur in the context of PTSD and can be noted as a diagnostic specifier. PTSD symptoms usually begin within three months of the trauma but there may be a delay in the full expression of symptoms.[22] Further, complex PTSD is an independent diagnosis in ICD-11 and may follow childhood trauma or persistent exposure to a traumatic environment in which escape is difficult or impossible.[23] It consists of the core PTSD symptoms, as well as affective dysregulation, negative self-concept and relational difficulties[5], and may be marked by treatment resistance or need for prolonged treatment course.[24]

The initial evaluation should include assessment of the severity, frequency and duration of re-experiencing, hyperarousal, emotional and cognitive symptoms, the degree of avoidance behaviour, and the extent of functional impairment. PTSD is commonly associated with other psychiatric symptoms, particularly anxiety, depressive and substance abuse symptoms, which therefore also deserve particular attention.[25]

STEP 2: COMPLICATIONS IN DIAGNOSIS IMPACTING PHARMACOTHERAPY

PTSD may be complicated in several ways, impacting on decisions about pharmacotherapy. Brief explanations of these complicating factors and their implications for pharmacotherapy follow:

a. **Severity:** Patients with severe symptoms may require brief hospitalisation to help contain symptoms. Acute administration of high-potency benzodiazepines (e.g., alprazolam, clonazepam) may be necessary. Slow-release preparations or benzodiazepines with longer half-lives (e.g., clonazepam) have the advantage of avoiding rebound anxiety between doses. Benzodiazepines are not, however, recommended in the long-term management of PTSD.[26,27]
b. **Melancholia:** Patients with PTSD often have comorbid depression, which usually also responds to first-line PTSD treatments such as the selective serotonin re-uptake inhibitors (SSRIs). Patients with melancholia

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Table 9.1. Diagnostic guidelines for post-traumatic stress disorder (adapted from ICD-11)

1. The person has been exposed to an event or situation (either short- or long-lasting) which is of an extremely threatening or horrific nature. This may include:
- Directly experiencing the traumatic event (e.g., natural or human-made disasters, combat, serious accidents, torture, sexual violence, terrorism, assault, acute life-threatening illness).
- Witnessing, in person, the event as it occurred to others.
- Learning that the event has occurred to a close family member or friend.
- Experiencing repeated or extreme exposure to aversive details of the traumatic event.

2. Following the traumatic event (or situation), a characteristic syndrome develops, lasting for at least several weeks and consisting of all three core elements; (1) re-experiencing the event, (2) avoidance behaviour and (3) heightened perception of threat.

3. Re-experiencing the traumatic event in the present – not just remembered, but experienced in the here and now. This occurs in the form of:
- Vivid, intrusive memories or images
- Flashbacks, ranging from mild (transient sense of the event occurring again) to severe (complete loss of awareness of present surroundings).
- Repetitive dreams or nightmares that are thematically related to the traumatic event(s).

Re-experiencing is typically accompanied by strong or overwhelming emotions (fear or horror) and strong physical sensations (physiological reactions). May occur in response to reminders of the event. Reflecting on or ruminating about the event and remembering feelings are not sufficient to meet the re-experiencing requirement.

4. Deliberate avoidance of reminders likely to produce re-experiencing of the traumatic event(s). This may take the form of:
- Active internal avoidance of thoughts and memories related to the event
- External avoidance of people, conversations, activities, or situations reminiscent of the event
- Change of environment to avoid reminders (e.g., a move to a different city or a change of job) in extreme cases.

5. Persistent perceptions of heightened, current threat may be expressed as:
- General hypervigilance
- Enhanced startle reaction to stimuli, such as unexpected noises
- Constantly guarding themselves against danger
- Feeling themselves or others close to them to be under immediate threat, either in specific situations or generally
- Adopting new behaviours designed to ensure safety (e.g., not sitting with their back to the door, repeatedly checking vehicles' rear-view mirrors)

6. Additional clinical features of PTSD may include:
- General dysphoria
- Dissociative symptoms
- Somatic complaints
- Suicidal ideation and behaviour
- Social withdrawal
- Excessive alcohol or drug use to avoid re-experiencing or manage emotional reactions
- Anxiety symptoms including panic
- Obsessions and compulsions in response to memories or reminders of the trauma

7. The emotional experience of individuals with PTSD commonly includes anger, shame, sadness, humiliation or guilt (including survivor guilt).

8. Duration of the disturbance (i.e., symptoms in Criteria 3, 4, 5 and 6) is more than one month.

9. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning (e.g., personal, family, educational).

10. The disturbance is not attributable to the physiological effects of a substance or another medical condition.

Table 9.2. Diagnostic guidelines for panic attack specifier (adapted from ICD-11)

A discrete episode of intense fear or apprehension, in which a number of the following symptoms develop rapidly and concurrently, and usually reach a peak within 10 minutes:
1. Palpitations, pounding heart, or increased heart rate
2. Sweating
3. Trembling or shaking
4. Sensations of shortness of breath or smothering
5. Feeling of choking
6. Chest pain or discomfort
7. Nausea or abdominal distress
8. Feeling dizzy, unsteady, lightheaded, or faint
9. Chills or hot flushes
10. Paraesthesias (numbness or tingling sensations)
11. Derealisation (feelings of unreality) or depersonalisation (being detached from oneself)
12. Fear of losing control or "going crazy"
13. Fear of imminent death
Panic attacks may be triggered by particular situations, or may appear out of the blue

appear to respond better to antidepressants and electroconvulsive therapy and less favourably to psychotherapy and placebo than do non-melancholic patients.[28,29] There is some evidence that older drugs, such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), may be more effective than selective serotonin reuptake inhibitors (SSRIs) in patients with depression accompanied by melancholic features, and hospitalised inpatients[30,31], although not all evidence is consistent.[29]

c. Alcohol and/or substance use: There is a strong association between PTSD and substance-use disorders (SUD).[32] Dual diagnosis is associated with higher rates of psychiatric comorbidity and more severe PTSD symptoms.[33] The relationship between PTSD and SUD is complex. Firstly, exposure to trauma has been found to play a role in the initiation and maintenance of SUD[34,35] and PTSD may lead to use of alcohol and other substances in order to self-medicate symptoms.[36] Secondly, patients with SUD may be at greater risk of trauma exposure and more vulnerable to developing PTSD.[37] Finally, there may be common environmental and genetic risk factors for both PTSD and SUD.[38,39]

Although it is ideal to detoxify patients prior to beginning pharmacotherapy, withdrawal of drugs, particularly central nervous system depressants, may be poorly tolerated because of the resulting additive physiologic arousal effects.[33] Psychotherapy of comorbid PTSD and substance use disorder has shown only modest efficacy.[40] Pharmacotherapy may also be necessary to treat the substance-use disorder and there is growing interest in agents that can target both disorders.[38,41,42] Randomised clinical trials suggest that SSRIs, SNRIs and some anticonvulsants may have efficacy for the treatment of PTSD and comorbid alcohol-use disorder.[41,43] Benzodiazepines are relatively contraindicated in these patients.[44]

d. Pregnancy, lactation, menopause: Pharmacotherapy should ideally be avoided during pregnancy and lactation. Nevertheless, where clinical considerations outweigh the risk of medication, such intervention should be considered after consultation with a specialist. Adverse-pregnancy-outcome studies can be difficult to interpret and it is not always clear whether outcomes observed are due to medications themselves or confounders such as the underlying mental illness.[45] SSRIs are generally considered safe first-line agents in pregnancy and there is currently no conclusive evidence of an association between treatment with these agents and increased risk for malformations, preterm birth, low birth weight or small-for-gestational-age births.[46] However, fluoxetine and paroxetine use in early pregnancy may be associated with a small increased risk for cardiovascular malformations, and initiation

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Table 9.3. Top-8 (for post-traumatic stress disorder)

The investigator should identify which traumatic event is the most bothersome and then how much each symptom has troubled the subject during the past week. **Event: .....**
1. Have you experienced painful images, thoughts or memories of the event which you could not get out of your mind even though you may have wanted to? 0 = not at all 1 = mild: rarely and/or not bothersome 2 = moderate: at least once a week and/or produces some distress 3 = severe: at least four times per week or moderately distressing 4 = extremely severe: daily or produces so much distress that patient cannot work or function socially
2. Does exposure to an event that reminds you of, or resembles, the event, cause you any physical response (eg, sweating, trembling, racing heart, nausea, hyperventilating, dizziness, etc)? 0 = not at all 1 = a little bit: infrequent or questionable 2 = somewhat: mildly distressing 3 = significant: causes much distress 4 = marked: very distressing; may have sought help because of the physical response (e.g., chest pain so severe that patients were sure they were having a heart attack)
3. Have you avoided places, people, conversations or activities that remind you of the event (e.g., movies, TV shows, certain places, meetings, funerals)? 0 = no avoidance 1 = mild: of doubtful significance 2 = moderate: definite avoidance of situations 3 = severe: very uncomfortable and avoidance affects life in some way 4 = extremely severe: house-bound, cannot go out to shops or restaurants, major functional restrictions
4. Have you experienced less interest (pleasure) in things that you used to enjoy? 0 = no loss of interest 1 = one or two activities less pleasurable 2 = several activities less pleasurable 3 = most activities less pleasurable 4 = almost all activities less pleasurable
5. Do you have less to do with other people than you used to? Do you feel estranged from other people? 0 = no problem 1 = feels detached/estranged, but still normal degree of contact with others 2 = sometimes avoids contact that would normally participate in 3 = definitely and patients usually avoid people with whom they would usually associate 4 = absolutely refuses or actively avoids all social contact
6. Can you have warm feelings/feel close to others? Do you feel numb? 0 = no problem 1 = mild: of questionable significance 2 = moderate: some difficulty expressing feelings 3 = severe: definite problems expressing feelings 4 = very severe: has no feelings, feels numb most of the time

Table 9.3. (continued)

7. Do you have to stay on guard? Are you watchful? Do you feel on edge? Do you have to sit with your back to the wall?
0 = no problem
1 = mild: occasional, not disruptive
2 = moderate: causes discomfort/feels on edge or watchful in some situations
3 = severe: causes discomfort/feels on edge or watchful in most situations
4 = very severe: causes extreme discomfort and/or alters life (feels constantly on guard/ socially impaired because of hypervigilance)

8. Do you startle easily? Do you have a tendency to jump? Is this a problem after unexpected noise, or if you hear or see something that reminds you of the trauma?
0 = no problem
1 = mild: occasional but not disruptive
2 = moderate: causes definite discomfort or an exaggerated startle response at least every two weeks
3 = severe: happens more than once a week
4 = extremely severe: so bad that the patient cannot function at work or socially

of these agents should be avoided in the first trimester.[46] The risk of persistent pulmonary hypertension of the newborn has been shown to be increased for infants exposed to SSRIs in late pregnancy, although clinically the absolute risk is low.[47]

e. **Comorbid medical disorders and medications:** Clinicians need to be aware of the multiple interactions between medications used in the treatment of PTSD, as well as of the impact of medication adverse effects on medical disorders.[48] Fortunately, certain SSRIs (e.g. sertraline and citalopram) have relatively few interactions with other medications, and the SSRIs as a class are well tolerated in most medical disorders.[49]

STEP 3: FIRST-LINE PHARMACOTHERAPY

In the algorithm (see Figure 9.1.), SSRIs or venlafaxine are suggested to be the first-line treatment of PTSD. There is now a great deal of evidence that SSRIs are both well tolerated and effective in PTSD.[6,26,44,50] Older studies support the use of tricyclic antidepressants and mono-amine oxidase inhibitors[51], but their relatively poor tolerability and safety profile means that these agents should not be used as first-line medications. Of the newer antidepressants, mirtazapine, a serotonergic and noradrenergic agent, has been shown to be superior to placebo in a single randomised control trial.[26,52]

There are few studies showing that any one SSRI is superior to another in the treatment of PTSD.[50] Of course, agents that have proved effective and tolerable in a particular individual in the past should be favoured in the present. Similarly, despite an absence of supporting empirical data, many clinicians suggest that family history of response to a particular antidepressant favours the choice of that agent.[53]

Important aspects of psycho-education regarding the SSRIs and SNRIs include the fact that these are not addictive, that despite being termed "antidepressants" they are effective in PTSD, that side effects are typically transient, that therapeutic response is relatively slow (two to four weeks) in onset, and that if one agent does not work another should be tried. Providing relevant information may help to improve treatment adherence.[6]

In PTSD, benzodiazepines do not appear to be effective[54,55] and they may, in fact, worsen treatment outcomes.[27,56]

Although ß-blockers are often prescribed by primary care practitioners for anxiety symptoms, there is insufficient evidence to include them as a first-line medication for PTSD.[57] There is currently insufficient evidence to support the acute administration of propranolol to prevent the development of PTSD.[6,57,58] Other adrenergic blockers may have a role as augmentation agents, as discussed below.

STEP 4: ASSESS RESPONSE TO TREATMENT

To determine response to medication, it is important to ask about change in those symptoms initially targeted for treatment. Side effects of the medication should also

be determined, with particular attention to those that patients may be reluctant to disclose (e.g., sexual dysfunction). It may be useful to complete symptom rating scales (see Table 9.3.) in order to help quantify response to medication, with repeated administration helping the clinician to gauge the trajectory of treatment response.[59]

Patients who are intolerant of a particular medication can, of course, be switched to another agent. Within the SSRIs, an alternative SSRI may be trialled when adverse effects are experienced.

When there is a poor response to medication, it is important to optimise dosage and duration of the medication. Studies have not shown significant differences in efficacy between higher and lower doses of SSRIs in the treatment of PTSD and treatment should be initiated at the lower end of the recommended range in order to minimise side effects.[60] If resistance to treatment is observed and initial low doses appear to be well tolerated, it is reasonable to consider increasing the dose.[61] Elderly patients generally require lower doses than do younger adults.[62]

Furthermore, response to SSRIs in PTSD may take up to 12 weeks and the proportion of patients who respond to treatment increases over time.[6] It is obviously important to give each patient a trial of medication that is of adequate duration.

STEP 5: MAINTENANCE OF RESPONSE AND AUGMENTATION STRATEGIES FOR PARTIAL RESPONSE

At the end of a clinical trial of optimal dose and duration, patients should be thoroughly re-assessed. There is growing recognition of the importance of residual anxiety symptoms in causing disability and predicting relapse, and of the consequent necessity of aiming for remission of symptoms as the endpoint of treatment.[63,64]

When the patient has a good response to medication, it is important to reinforce the necessity to the patient for continuing the medication at the therapeutic dose despite this improvement. Guidelines for maintenance therapy of PTSD have become increasingly conservative, favouring longer courses of medication, in view of the safety of modern antidepressant agents and the likelihood of relapse in patients with an untreated chronic illness.[6] In chronic PTSD, it is recommended that treatment be continued for at least 12-24 months before gradual tapering.[6,44] The presence of complex PTSD may necessitate longer treatment duration.[14] Cognitive-behavioural therapy may be useful during medication withdrawal in order to maintain gains, although more research on the optimal combination and sequencing of pharmacotherapy and psychotherapy in PTSD is needed.

When there is a partial response despite an optimum trial of medication, it may be useful to consider an augmenting agent. Despite a large proportion of patients failing to respond to first-line PTSD treatments, there are relatively few data on augmentation and switching strategies. Augmentation offers the advantage of retaining any possible gains from the first agent, but the potential disadvantages of polypharmacy (more side effects, drug interactions).[65] There is some promising evidence to support the use of psychotherapy augmentation in the treatment of PTSD although further large, randomised control trials are needed.[15,66-68]

In PTSD, a range of pharmacological augmentation strategies has been suggested, but few strategies have been studied in controlled trials.[50] The α1-adrenergic antagonist prazosin has been found to reduce insomnia, nightmares and other PTSD symptoms.[50,69-71] There is mixed evidence for the efficacy of augmentation with antipsychotic agents in non-responders to first-line agents.[61,72] There is evidence supporting augmentation with the atypical antipsychotic agents risperidone and olanzapine, particularly in combat-related traumas.[73-76] A recent review confirmed evidence of benefit for risperidone as an augmentation agent[50], and is also recommended in the NICE guidelines in this context.[14] Further research in this area is needed. In the interim, specialist consultation should be sought in such cases.

STEP 6: FAILURE TO RESPOND

When PTSD does not respond to a clinical trial of optimal dose and duration, it is useful to re-assess a number of factors. The presence of certain features may impact the choice of the subsequent intervention.

a. **Adherence:** Clinicians often over-estimate the treatment adherence of their patients

and it is often useful to check with patients and their families whether medication is being taken as prescribed. Many patients worry that medication is addictive or a "crutch".

b. **Comorbid substance use:** In patients who fail to respond to pharmacotherapy, the possibility of comorbid substance use should again be considered. Self-medication with alcohol and other substances is particularly common in PTSD. Specialist input regarding dual-diagnosis management may be needed. There is some evidence that topiramate may be effective in PTSD with comorbid alcohol-use disorder.[43]

c. **Comorbid personality disorders:** Although SSRIs may be useful, additional interventions such as psychotherapy may be crucial in patients with PTSD and comorbid personality disorder. While improvement in PTSD symptoms may reduce maladaptive behaviour in comorbid personality disorder, the personality disorder itself may need to be a major target of treatment.

d. **Underlying medical disorder:** PTSD patients who fail to respond to medication should be thoroughly re-assessed for an underlying medical disorder.

e. **Pharmacokinetic issues:** Drug-drug interactions may result in a subtherapeutic dose of the prescribed antidepressant.

f. **Psychosocial issues:** Psychosocial circumstances that continue to complicate the course of PTSD need to be assessed, as these may necessitate appropriate intervention. PTSD may be associated with disruptions in interpersonal relationships, altered perceptions of the self and others, survivor guilt, and so on, which require specific intervention.

STEP 7: TREATMENT RESISTANCE

After the failure of an adequate clinical trial of medication in a patient where re-assessment sheds no light on any further unresolved factors, a different evidence-based agent should be used. It is often advisable to switch classes of medication. It is also possible that switching from one SSRI to another may be useful. Patients who have failed to respond to SSRIs can be switched to venlafaxine which has good supporting evidence in the treatment of PTSD.[26,50] Mirtazapine, TCAs (amitriptyline, imipramine) or MAOIs (phenelzine) can be considered as third-line antidepressant agents.[6] There have been few trials of antipsychotic monotherapy; currently there is evidence of efficacy for risperidone[77,78] and olanzapine[79] and these can also be considered as third-line agents. The randomised controlled trial evidence for anticonvulsant monotherapy is mixed and further trials are warranted.[80-83] Ketamine has also been studied in PTSD and has shown some promising results, although findings are mixed.[84,85] Further research is required before it can be adopted as routine practice. Finally, augmentation strategies can sometimes be useful in patients who have not responded to multiple single agents.

If all avenues have been thoroughly explored, a second opinion by an expert is indicated. Medication trials that ended prematurely or that did not use optimal dosing can be repeated. It may ultimately be necessary to revert to the regimen on which the patient demonstrated the best response.

ADDITIONAL READING

1. Baldwin DS, Anderson IM, Nutt DJ, *et al*. Evidence-based pharmacological treatment of anxiety disorders, posttraumatic stress disorder and obsessive-compulsive disorder: A revision of the 2005 guidelines from the British Association for Psychopharmacology. J Psychopharmacol. 2014;28(5):403-439.
2. Ballenger JC, Davidson JR, Lecrubier Y, *et al*. Consensus statement on posttraumatic stress disorder from the International Consensus Group on Depression and Anxiety. J Clin Psychiatry. 2000;61. Suppl 5:60-66.
3. Bandelow B, Zohar J, Hollander E, *et al*. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and posttraumatic stress disorders – first revision. World J Biol Psychiatry. 2008;9(4):248-312.
4. Bisson JI, Roberts NP, Andrew M, *et al*. Psychological therapies for chronic posttraumatic stress disorder (PTSD) in adults. Cochrane Database Syst Rev. 2013(12): CD003388.
5. Cloitre M. Effective psychotherapies for posttraumatic stress disorder: A review and critique. CNS Spectr. 2009;14(1 Suppl 1):32-43.
6. Connolly SD, Bernstein GA, Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with anxiety disorders. J Am Acad Child Adolesc Psychiatry. 2007;46(2):267-283.
7. Hetrick SE, Purcell R, Garner B, *et al*. Combined pharmacotherapy and psychological therapies for post traumatic stress disorder (PTSD). Cochrane Database Syst Rev. 2010(7):CD007316.

8. Hoskins MD, Bridges J, Sinnerton R, *et al*. Pharmacological therapy for post-traumatic stress disorder: A systematic review and meta-analysis of monotherapy, augmentation and head-to-head approaches. European Journal of Psychotraumatology. 2021 Jan 1;12(1):1802920.
9. Ipser JC, Carey P, Dhansay Y, *et al*. Pharmacotherapy augmentation strategies in treatment-resistant anxiety disorders. Cochrane Database Syst Rev. 2006(4):CD005473.
10. Ipser JC, Stein DJ, Hawkridge S, *et al*. Pharmacotherapy for anxiety disorders in children and adolescents. Cochrane Database Syst Rev 2009(3):CD005170.
11. National Institute for Health and Care Excellence. Post-traumatic stress disorder [Internet]. [London]: NICE; 2018 [cited 2022 Jun 10]. (NICE guideline [NG116]). Available from: https://www.nice.org.uk/guidance/ng116.
12. Williams T, Phillips NJ, Stein DJ, *et al*. Pharmacotherapy for post traumatic stress disorder (PTSD). Cochrane Database of Systematic Reviews. 2022(3):CD002795.

REFERENCES

1. Ng LC, Stevenson A, Kalapurakkel SS, *et al*. National and Regional Prevalence of Posttraumatic Stress Disorder in Sub-Saharan Africa: A Systematic Review and Meta-Analysis. PLOS Medicine. 2020 May 15;17(5):e1003090.
2. Jellestad L, Vital NA, Malamud J, *et al*. Functional Impairment in Posttraumatic Stress Disorder: A Systematic Review and Meta-Analysis. Journal of Psychiatric Research. 2021 Apr 1;136:14-22.
3. Koenen KC, Ratanatharathorn A, Ng L, *et al*. Posttraumatic stress disorder in the World Mental Health Surveys. Psychol Med. 2017 Oct;47(13):2260-74.
4. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. Washington, DC: American Psychiatric Publishing; 2013.
5. World Health Organization. ICD-11: International classification of diseases (11th revision). 11th ed. Geneva: WHO; 2019.
6. Baldwin DS, Anderson IM, Nutt DJ, *et al*. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: A revision of the 2005 guidelines from the British Association for Psychopharmacology. J Psychopharmacol. 2014 May;28(5):403-39.
7. Bisson JI, Roberts NP, Andrew M, *et al*. Psychological therapies for chronic post-traumatic stress disorder (PTSD) in adults. Cochrane Database Syst Rev. 2013(12):CD003388.
8. McLean CP, Levy HC, Miller ML, *et al*. Exposure Therapy for PTSD: A Meta-Analysis. Clin Psychol Rev. 2022 Feb;91:102115.
9. Bonfils KA, Tennity CL, Congedo BA, *et al*. Functional Outcomes from Psychotherapy for People with Posttraumatic Stress Disorder: A Meta-Analysis. J Anxiety Disord. 2022 May 10;89:102576.
10. Rose S, Bisson J, Churchill R, *et al*. Psychological debriefing for preventing post traumatic stress disorder (PTSD). Cochrane Database Syst Rev. 2002(2):CD000560.
11. Roberts NP, Kitchiner NJ, Kenardy J, *et al*. Multiple session early psychological interventions for the prevention of post-traumatic stress disorder. Cochrane Database Syst Rev. 2019(8):CD006869.
12. Roberts NP, Kitchiner NJ, Kenardy J, *et al*. Early psychological interventions to treat acute traumatic stress symptoms. Cochrane Database Syst Rev. 2010(3):CD007944.
13. Lewis C, Roberts NP, Andrew M, *et al*. Psychological Therapies for Post-Traumatic Stress Disorder in Adults: Systematic Review and Meta-Analysis. Eur J Psychotraumatol. 2020 Mar 10;11(1):1729633.
14. National Institute for Health and Care Excellence. Post-traumatic stress disorder [Internet]. [London]: NICE; 2018 [cited 2022 Jun 10]. (NICE guideline [NG116]). Available from: https://www.nice.org.uk/guidance/ng116.
15. Hetrick SE, Purcell R, Garner B, *et al*. Combined pharmacotherapy and psychological therapies for post traumatic stress disorder (PTSD). Cochrane Database Syst Rev. 2010(7):CD007316.
16. Storm MP, Christensen KS. Comparing Treatments for Post-Traumatic Stress Disorder – a Systematic Review. Dan Med J. 2021 Aug 27;68(9):A09200643.
17. Kuzma JM, Black DW. Integrating pharmacotherapy and psychotherapy in the management of anxiety disorders. Curr Psychiatry Rep. 2004;6(4):268-73.
18. Pratchett LC, Daly K, Bierer LM, *et al*. New approaches to combining pharmacotherapy and psychotherapy for posttraumatic stress disorder. Expert Opin Pharmacother. 2011 Oct;12(15):2339-54.
19. Ipser JC, Stein DJ, Hawkridge S, *et al*. Pharmacotherapy for anxiety disorders in children and adolescents. Cochrane Database Syst Rev. 2009(3):CD005170.
20. Bandelow B, Sher L, Bunevicius R, *et al*. Guidelines for the pharmacological treatment of anxiety disorders, obsessive-compulsive disorder and post-traumatic stress disorder in primary care. Int J Psychiatry Clin Pract. 2012;16(2):77-84.
21. Brewin CR, Andrews B, Valentine JD. Meta-Analysis of Risk factors for Post-Traumatic Stress Disorder in Trauma-Exposed Adults. J Consult Clin Psychol. 2000;68(5):748-66.

22. Shalev AY. Post-traumatic stress disorder and stress-related disorders. Psychiatr Clin North Am. 2009;32(3):687-704.
23. Herman JL. Complex PTSD: A syndrome in survivors of prolonged and repeated trauma. Journal of Traumatic Stress. 1992;5(3):377-91.
24. Nestgaard Rød Å, Schmidt C. Complex PTSD: What is the clinical utility of the diagnosis? Eur J Psychotraumatol. 12(1):2002028.
25. Stein DJ, Craske MG, Rothbaum BO, *et al*. The clinical characterization of the adult patient with an anxiety or related disorder aimed at personalization of management. World Psychiatry. 2021 Oct;20(3):336-56.
26. Williams T, Phillips NJ, Stein DJ, *et al*. Pharmacotherapy for post traumatic stress disorder (PTSD). Cochrane Database Syst Rev. 2022(3):CD002795.
27. Campos B, Vinder V, Passos RBF, *et al*. To BDZ or Not to BDZ? That is the Question! Is There Reliable Scientific Evidence for or against Using Benzodiazepines in the Aftermath of Potentially Traumatic Events for the Prevention of PTSD? A Systematic Review and Meta-Analysis. J Psychopharmacol. 2022 Apr;36(4):449-59.
28. Brown WA. Treatment response in melancholia. Acta Psychiatr Scand Suppl. 2007(433):125-9.
29. Sneed JR, Reinlieb ME, Rutherford BR, *et al*. Antidepressant treatment of melancholia in older adults. Am J Geriatr Psychiatry. 2014 Jan;22(1):46-52.
30. Anderson IM. SSRIS Versus Tricyclic Antidepressants in Depressed Inpatients: A Meta-Analysis of Efficacy and Tolerability. Depress Anxiety. 1998;7(Suppl 1):11-7.
31. Perry PJ. Pharmacotherapy for major depression with melancholic features: Relative efficacy of tricyclic versus selective serotonin re-uptake inhibitor antidepressants. J Affect Disord. 1996;39(1):1-6.
32. Pietrzak RH, Goldstein RB, Southwick SM, *et al*. Prevalence and Axis I comorbidity of full and partial posttraumatic stress disorder in the United States: Results from Wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions. J Anxiety Disord. 2011 Apr;25(3):456-65.
33. Jacobsen LK, Southwick SM, Kosten TR. Substance use disorders in patients with post-traumatic stress disorder: A review of the literature. Am J Psychiatry. 2001;158(8):1184-90.
34. Keyes KM, Hatzenbuehler ML, Hasin DS. Stressful life experiences, alcohol consumption, and alcohol use disorders: The epidemiologic evidence for four main types of stressors. Psychopharmacology (Berl). 2011;218(1):1-17.
35. Logrip ML, Zorrilla EP, Koob GF. Stress modulation of drug self-administration: Implications for addiction comorbidity with post-traumatic stress disorder. Neuropharmacology. 2012;62(2):552-64.
36. Khantzian EJ. The self-medication hypothesis of substance use disorders: A reconsideration and recent applications. Harv Rev Psychiatry. 1997;4(5):231-44.
37. Hildebrand A, Behrendt S, Hoyer J. Treatment Outcome in Substance Use Disorder Patients with and without Comorbid Post-Traumatic Stress Disorder: A Systematic Review. Psychother Res. 2014;1-18.
38. Norman SB, Myers US, Wilkins KC, *et al*. Review of biological mechanisms and pharmacological treatments of comorbid PTSD and substance use disorder. Neuropharmacology. 2012;62(2):542-51.
39. Sheerin CM, Bountress KE, Meyers JL, *et al*. Shared molecular genetic risk of alcohol dependence and posttraumatic stress disorder (PTSD). Psychol Addict Behav. 2020 Aug;34(5):613-9.
40. Roberts NP, Lotzin A, Schäfer I. A Systematic Review and Meta-Analysis of Psychological Interventions for Comorbid Post-Traumatic Stress Disorder and Substance Use Disorder. Eur J Psychotraumatol. 2022;13(1):2041831.
41. Ipser JC, Wilson D, Akindipe TO, *et al*. Pharmacotherapy for anxiety and comorbid alcohol use disorders. Cochrane Database Syst Rev. 2015(1):CD007505.
42. Verplaetse TL, McKee SA, Petrakis IL. Pharmacotherapy for co-occurring alcohol use disorder and post-traumatic stress disorder: Targeting the opioidergic, noradrenergic, serotonergic, and GABAergic/glutamatergic systems. Alcohol Res. 2018;39(2):193-205.
43. Batki SL, Pennington DL, Lasher B, *et al*. Topiramate treatment of alcohol use disorder in veterans with posttraumatic stress disorder: A randomized controlled pilot trial. Alcohol Clin Exp Res. 2014 Aug;38(8):2169-77.
44. Bandelow B, Zohar J, WFSBP Task Force on Treatment Guidelines for Anxiety, Obsessive-Compulsive and Post-Traumatic Stress Disorders, *et al*. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders – first revision. World J Biol Psychiatry. 2008;9(4):248-312.
45. Spinelli M. Antidepressant treatment during pregnancy. Am J Psychiatry. 2012;169(2):121-4.
46. Zhang T-N, Gao S-Y, Shen Z-Q, *et al*. Use of Selective Serotonin Re-Uptake Inhibitors in the First Trimester and Risk of Cardiovascular-Related Malformations: A Meta-Analysis of Cohort Studies. Sci Rep. 2017 Feb 21;7:43085.
47. Grigoriadis S, Vonderporten EH, Mamisashvili L, *et al*. Prenatal Exposure to Antidepressants and Persistent Pulmonary Hypertension of the Newborn: Systematic Review and Meta-Analysis. BMJ. 2014;348:f6932.

48. Spina E, de Leon J. Clinically relevant interactions between newer antidepressants and second-generation antipsychotics. Expert Opin Drug Metab Toxicol. 2014 May;10(5):721-46.
49. Evans DL, Charney DS, Lewis L, *et al*. Mood disorders in the medically ill: Scientific review and recommendations. Biol Psychiatry. 2005;58(3):175-89.
50. Hoskins MD, Bridges J, Sinnerton R, *et al*. Pharmacological Therapy for Post-Traumatic Stress Disorder: A Systematic Review and Meta-Analysis of Monotherapy, Augmentation and Head-to-Head Approaches. European Journal of Psychotraumatology. 2021 Jan 1;12(1):1802920.
51. Hageman I, Andersen HS, Jorgensen MB. Post-traumatic stress disorder: A review of psychobiology and pharmacotherapy. Acta Psychiatr Scand. 2001;104(6):411-22.
52. Davidson JR, Weisler RH, Butterfield MI. Mirtazapine vs. placebo in post-traumatic stress disorder: A pilot trial. Biol Psychiatry. 2003;53(2):188-91.
53. Zetin M, Hoepner CT, Bjornson L. Rational antidepressant selection: Applying evidence-based medicine to complex real-world patients. Psychopharmacol Bull. 2006;39(1):38-104.
54. Braun P, Greenberg D, Dasberg H, *et al*. Core symptoms of post-traumatic stress disorder unimproved by alprazolam treatment. J Clin Psychiatry. 1990;51(6):236-8.
55. Cates ME, Bishop MH, Davis LL, *et al*. Clonazepam for treatment of sleep disturbances associated with combat-related post-traumatic stress disorder. Ann Pharmacother. 2004;38(9):1395-9.
56. Guina J, Rossetter SR, DeRhodes BJ, *et al*. Benzodiazepines for PTSD: A Systematic Review and Meta-Analysis. J Psychiatr Pract. 2015 Jul;21(4):281-303.
57. Young C, Butcher R. Propranolol for post-traumatic stress disorder: A review of clinical effectiveness [internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2020 [cited 2022 May 24]. (CADTH Rapid Response Reports). Available from: http://www.ncbi.nlm.nih.gov/books/NBK562942/
58. Amos T, Stein DJ, Ipser JC. Pharmacological interventions for preventing posttraumatic stress disorder (PTSD). Cochrane Database Syst Rev. 2014(7):CD006239.
59. Romba C, Lavigne J, Walkup J, *et al*. Measurement-based care in the treatment of anxiety. Child Adolesc Psychiatr Clin N Am. 2020 Oct;29(4):645-61.
60. Ipser JC, Stein DJ. Evidence-based pharmacotherapy of posttraumatic stress disorder (PTSD). Int J Neuropsychopharmacol. 2012;15(6):825-40.
61. Ipser JC. Pharmacotherapy augmentation strategies in treatment-resistant anxiety disorders. Cochrane Database Syst Rev. 2006(4):CD005473.
62. Marshall LL, Hayslett RL. Post-traumatic stress disorder in middle age and beyond. Sr Care Pharm. 2021 Apr 1;36(4):191-207.
63. Ballenger JC. Treatment of anxiety disorders to remission. J Clin Psychiatry. 2001;12:5-9.
64. Larsen SE, Fleming CJE, Resick PA. Residual symptoms following empirically supported treatment for PTSD. Psychol Trauma. 2019 Feb;11(2):207-15.
65. Rush AJ, Warden D, Wisniewski SR, *et al*. STAR*D: Revising conventional wisdom. CNS Drugs. 2009;23(8):627-47.
66. Otto MW, Hinton D, Korbly NB, *et al*. Treatment of pharmacotherapy-refractory posttraumatic stress disorder among Cambodian refugees: A pilot study of combination treatment with cognitive behavior therapy vs sertraline alone. Behav Res Ther. 2003;41:1271-6.
67. Rothbaum BO, Cahill SP, Foa EB, *et al*. Augmentation of sertraline with prolonged exposure in the treatment of posttraumatic stress disorder. J Trauma Stress. 2006;19(5):625-38.
68. Schneier FR, Neria Y, Pavlicova M, *et al*. Combined prolonged exposure therapy and paroxetine for PTSD related to the World Trade Center attack: A randomized controlled trial. Am J Psychiatry. 2012;169(1):80-8.
69. Raskind MA, Peskind ER, Hoff DJ, *et al*. A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with posttraumatic stress disorder. Biol Psychiatry. 2007;61(8):928-34.
70. Raskind MA, Peskind ER, Kanter ED, *et al*. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: A placebo-controlled study. Am J Psychiatry. 2003;160(2):371-3.
71. Taylor HR, Freeman MK, Cates ME. Prazosin for treatment of nightmares related to post-traumatic stress disorder. Am J Health Syst Pharm. 2008;65(8):716-22.
72. Connell R, Zeier K, Thomas CJ. A review of atypical antipsychotics and their utility in post-traumatic stress disorder. Mental Health Clinician. 2013 Jan 1;2(7):187-94.
73. Stein MB, Kline NA, Matloff JL. Adjunctive olanzapine for SSRI-resistant combat-related PTSD: A double-blind, placebo-controlled study. Am J Psychiatry. 2002;159(10):1777-9.
74. Hamner MB, Faldowski RA, Ulmer HG, *et al*. Adjunctive risperidone treatment in post-traumatic stress disorder: A preliminary controlled trial of effects on comorbid psychotic symptoms. Int Clin Psychopharmacol. 2003;18(1):1-8.
75. Monnelly EP, Ciraulo DA, Knapp C, *et al*. Low-dose risperidone as adjunctive therapy for irritable aggression in post-traumatic stress disorder. J Clin Psychopharmacol. 2003;23(2):193-6.

76. Bartzokis G, Lu PH, Turner J, *et al*. Adjunctive risperidone in the treatment of chronic combat-related posttraumatic stress disorder. Biol Psychiatry. 2005;57(5):474-9.
77. Padala PR, Madison J, Monnahan M, *et al*. Risperidone monotherapy for posttraumatic stress disorder related to sexual assault and domestic abuse in women. Int Clin Psychopharmacol. 2006;21(5):275-80.
78. Reich DB, Winternitz S, Hennen J, *et al*. A preliminary study of risperidone in the treatment of post-traumatic stress disorder related to childhood abuse in women. J Clin Psychiatry. 2004;65(12):1601-6.
79. Carey P, Suliman S, Ganesan K, *et al*. Olanzapine monotherapy in post-traumatic stress disorder: Efficacy in a randomized, double-blind, placebo-controlled study. Hum Psychopharmacol. 2012;27(4):386-91.
80. Hertzberg MA, Butterfield MI, Feldman ME, *et al*. A preliminary study of lamotrigine for the treatment of post-traumatic stress disorder. Biol Psychiatry. 1999;45(9):1226-9.
81. Davidson JRT, Brady K, Mellman TA, *et al*. The efficacy and tolerability of tiagabine in adult patients with post-traumatic stress disorder. J Clin Psychopharmacol. 2007;27(1):85-8.
82. Tucker P, Trautman RP, Wyatt DB, *et al*. Efficacy and safety of topiramate monotherapy in civilian post-traumatic stress disorder: A randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2007;68(2):201-6.
83. Davis LL, Davidson JRT, Ward LC, *et al*. Divalproex in the treatment of post-traumatic stress disorder: A randomized, double-blind, placebo controlled trial in a veteran population. J Clin Psychopharmacol. 2008;28(1):84-8.+
84. Du R, Han R, Niu K, *et al*. The Multivariate Effect of Ketamine on PTSD: Systematic Review and Meta-Analysis. Front Psychiatry. 2022;13:813103. s
85. Jumaili WA, Trivedi C, Chao T, *et al*. The safety and efficacy of ketamine NMDA receptor blocker as a therapeutic intervention for PTSD review of a randomized clinical trial. Behav Brain Res. 2022 Apr 29;424:113804.

10: Insomnia Disorder

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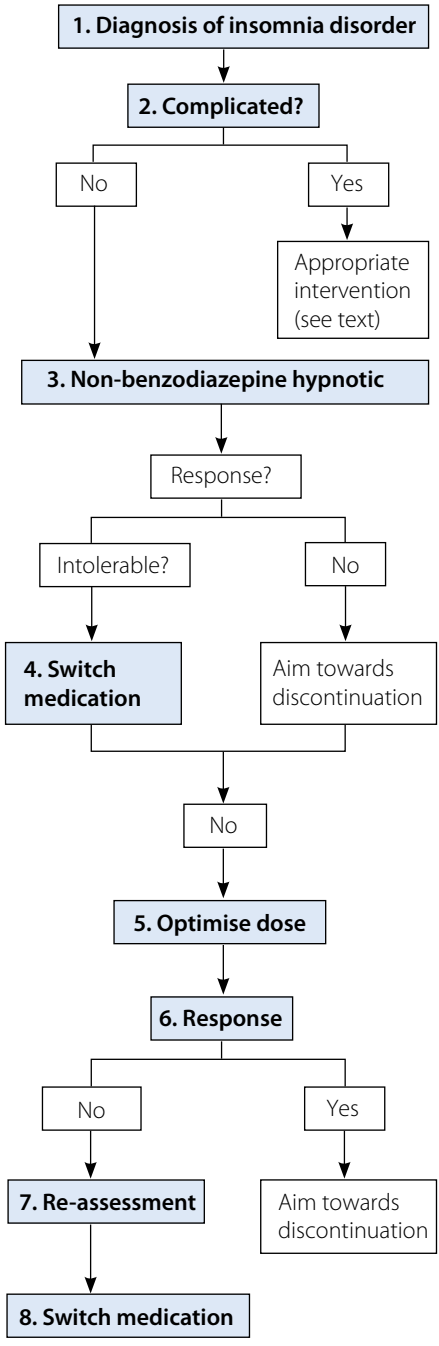
Insomnia is an extremely common symptom, accounting for over five million primary care outpatient consultations per year in the United States.[1] There is growing evidence that chronic insomnia is associated with significant morbidity, including impairment in cognitive and motoric performance, decreased work productivity, increased use of medical services, and greater risk for serious accidents.[2-4] Finally, persistent insomnia is a risk factor for depression.[5]

In this chapter, we focus on insomnia disorder. According to ICD-11 guidelines (see Table 10.1.), this disorder is a type of sleep-wake disorder characterised by difficulty in initiating or maintaining sleep, which may be short-term (lasting less than three months) or chronic (lasting more than three months). Insomnia disorder may be divided into that characterised by objective sleep architecture abnormalities on polysomnography (similar to the construct of psychophysiological insomnia), and that in which the person does not subjectively feel refreshed despite objective evidence of normal sleep (sleep state misperception).

As in the rest of this volume, our focus here is on pharmacotherapy. Nevertheless, given that insomnia is often a symptom rather than a diagnosis, assessment is a particularly crucial step. Furthermore, cognitive-behavioural interventions are efficacious[6-8], and combined cognitive-behavioural and pharmacological intervention may be particularly so.[9] Behavioural intervention for insomnia includes cognitive-behaviour therapy (CBT-I)[10], a general set of psycho-educational instructions known

Figure 10.1. Algorithm for pharmacotherapy of insomnia disorder



as "sleep hygiene", as well as specific techniques such as stimulus control and planned sleep deprivation. Although effective as an adjunct to other treatments, improving sleep hygiene alone may be ineffective for many patients.[11] We list some suggestions that can be provided to primary care patients (see Table 10.2.).

STEP 1: DIAGNOSIS OF INSOMNIA DISORDER

Insomnia disorder is a diagnosis of exclusion. First, underlying psychiatric and medical disorders must be ruled out. In this context, it is important to emphasise the association between insomnia and mood disorders (depression, mania), anxiety and related disorders (generalised anxiety disorder, post-traumatic stress disorder, obsessive-compulsive disorder), neurocognitive disorders (dementia), and attention deficit hyperactivity disorder. Similarly, insomnia is often associated with particular medications (e.g., mono-amine oxidase inhibitors, caffeine or methylphenidate) or with general medical disorders (e.g., pain disorders, hypoxaemia).

Second, other sleep disorders associated with insomnia must be ruled out. These

Table 10.1. Clinical guidelines for insomnia disorder (adapted from ICD-11)

1. Insomnia disorders are characterised by complaint of persistent difficulty with one or more of: • Sleep initiation • Sleep duration • Sleep consolidation • Sleep quality
2. The sleep disturbance occurs despite adequate opportunity and circumstances for sleep
3. The sleep difficulty results in some form of daytime impairment.
4. The sleep difficulty results in daytime symptoms which may include fatigue, depressed mood or irritability, general malaise and cognitive impairment.
5. The sleep difficulty occurs despite adequate opportunity for sleep.
6. If sleep-related symptoms are present in the absence of daytime impairment, insomnia disorder does not apply.
7. Chronic insomnia is defined by sleep disturbance and daytime symptoms at least several times per week for at least 3 months. Some may show an episodic course, with recurrent episodes of sleep/wake difficulties lasting several weeks at a time over several years.
8. Short-term insomnia is defined by difficulty initiating or maintaining sleep for less than 3 months duration.
9. If the insomnia is due to another sleep-wake disorder, a mental disorder, another medical condition, or a substance or medication, chronic or short-term insomnia should only be diagnosed if the insomnia is an independent focus of clinical attention.

Table 10.2. Sleep hygiene with stimulus control

• Exercise regularly, but not just before bedtime
• Avoid sedatives (e.g., alcohol) just before bedtime
• Avoid stimulants (e.g., nicotine, caffeine) just before bedtime
• Eat only a light snack just before bedtime
• Relaxing routine (e.g., hot bath) just before bedtime
• Ensure that the room/bed is quiet/comfortable
• Use the bed only for sleeping and for sex
• Avoid daytime napping (except in the elderly)
• Get up at the same time each day (even if tired)
• Don't watch the clock after going to bed
• If not asleep within 20 minutes, do low-energy activity in other room (e.g., reading) until tired

include periodic limb movement disorder, restless legs syndrome, sleep-disordered breathing, circadian rhythm disturbances, and parasomnias (somnambulism, sleep terrors). In children, disturbed sleep often reflects parasomnias.[12,13] In the elderly, there are normal age-related changes in sleep pattern.[14,15]

In general practice, a comprehensive medical and psychiatric history is particularly useful to rule out disorders associated with insomnia. The pharmacotherapy of insomnia secondary to mood and anxiety disorders essentially comprises the treatment of those disorders.[7,16,17] The treatment of those disorders is described elsewhere in this volume (Chapters 5-7), but it may be worth emphasising that antidepressants rather than benzodiazepines should be the first-line choice; antidepressants are more effective in the treatment of depression, PTSD and anxiety disorders. Similarly, in dementia, benzodiazepines may have significant adverse events.[18,19] Even in patients with pain, the antidepressant amitriptyline has both analgesic and sedative effects.[20,21]

A comprehensive evaluation of sleep symptoms is also necessary, as each of the different sleep disorders requires its own treatment. For example, in restless legs syndrome, patients describe peripheral sensations that are relieved by movement, and this disorder may respond to treatment with dopamine agonists or other agents. In circadian rhythm sleep disorder, there is a mismatch between the person's circadian sleep-wake pattern and the sleep-wake patterns required by their environment. For example, in the delayed sleep phase subtype of this disorder, patients fall asleep late and then wake up late after otherwise normal sleep; such patients may respond to light therapy and perhaps to melatonin.[22,23] In the jet-lag subtype, patients are sleepy or alert at an inappropriate time relative to local time after repeated travel across time zones; night-time melatonin may be useful in preventing such symptoms.[24,25]

Unfortunately, some sleep disorders are not readily diagnosable on history alone. For example, although patients with obstructive sleep apnoea may present with specific risk factors (e.g., obesity) and may have specific symptoms (e.g., snoring, daytime somnolence), patients with sleep-disorder breathing may not be aware of apnoea/hypnoea.[26] Similarly, although partners may be aware of movements, patients with periodic limb movement disorder may not be aware of their movements. Both groups of patients may have secondary depression/anxiety.

Polysomnography may therefore play a useful role in the assessment of insomnia.[27]

STEP 2: COMPLICATIONS IN DIAGNOSIS IMPACTING PHARMACOTHERAPY

Insomnia disorder can be complicated by several different factors that impact on pharmacotherapy decisions:

a. **Adjustment disorder/bereavement/other focus of clinical attention:** Any of these disorders may have been the trigger of the insomnia and may continue to be present. It is clearly important to address the relevant issues in a supportive way before considering the use of medications for symptomatic control. Antidepressants (at standard antidepressant doses) should be favoured if it is suspected that a mood disorder has emerged.

b. **Alcohol and/or substance use:** Patients with insomnia often use alcohol, benzodiazepines, or other substances in an attempt to control their symptoms. While withdrawal of such substances may well be indicated, in the short term, this may run the risk of exacerbating insomnia.[28] Psychoeducation is clearly important. Slow and gradual tapering of the substance should be encouraged, and may be facilitated by switching to a long half-life benzodiazepine. In the interim, treatment with sedative, non-dependence-causing medications (e.g., trazodone) may be helpful.[28]

c. **Pregnancy/lactation:** Pregnant patients frequently complain of disturbed sleep. Similarly, the care of a young infant often results in disturbed sleep. Pharmacotherapy should ideally be avoided during pregnancy and lactation. Nevertheless, where clinical considerations outweigh the risk of medication, such intervention should be considered after consultation with a specialist. Benzodiazepine use during pregnancy is not contraindicated, but has been associated with an increased risk of cleft palate, preterm delivery low birth weight and neonatal withdrawal syndrome.[29,30] If used, the lowest effective dose of the benzodiazepine should be prescribed for the shortest possible duration, and high

peak concentrations should be avoided by dividing the daily dosage into two or three doses.

d. **Comorbid medical disorders and medications:** It is absolutely crucial not to treat insomnia secondary to hypoxaemia (e.g., obstructive sleep apnoea) with an agent that suppresses respiratory function.[31,32] Furthermore, clinicians need to be aware of the interactions of medications used in the treatment of insomnia and the treatment of other disorders, as well as of the impact of medication adverse effects on medical disorders. In patients with impaired liver function, hepatically metabolised medications are started at a lower dose.

e. **Comorbid personality disorder:** Patients with maladaptive personality traits (for example, as seen in borderline personality disorder), may experience protracted sleep symptoms[33,34] Benzodiazepines are relatively contraindicated in patients with borderline personality disorder, as they may promote disinhibition.[35,36] Where clinical judgment reveals personality traits suggestive of possible vulnerability to future benzodiazepine dependence, these agents should be avoided.

STEP 3: FIRST-LINE PHARMACOTHERAPY

In our algorithm for insomnia disorder (see Figure 10.1.), we suggest that the first-line medication treatment of insomnia disorder in adults is a non-benzodiazepine GABA-A receptor agonist. The non-benzodiazepine hypnotics available on the South African market comprise zolpidem (an imidazopyridine) and zopiclone (a cyclopyrrolone). These agents have a pharmacological mechanism of action similar to the benzodiazepines, but have largely replaced benzodiazepines as first-line mediations in primary care settings, and appear less likely to cause dependency.[20,22] However, clinicians should be aware that they appear to be associated with daytime cognitive slowing, impairments in driving ability, reductions in psychomotor speed and with night-time changes in sleep architecture, especially at higher doses.[37,38] Zolpidem has a shorter half-life (three hours) than zopiclone (six hours), so theoretically the former may have some advantage in reducing daytime side effects, while the latter may provide better coverage for terminal insomnia.

A short-acting benzodiazepine can be used as an alternative to zolpidem or zopiclone, using drugs with shorter half-lives at low doses and in limited quantities, and with intermittent and strategic prescribing.[39] It is important to remind all patients (and particularly those driving and working with machinery) of possible daytime impairment when using long-acting benzodiazepines or non-benzodiazepine hypnotics.[38]

Although not as well studied for insomnia disorder as are the hypnotics, certain antidepressants may improve insomnia; there is limited evidence for the efficacy of trazodone, mirtazapine, mianserin, amitriptyline, and paroxetine.[22] Trazodone runs the risk of priapism in men, but this is not typically seen with the low doses used in insomnia.[40] These medications are particularly useful where co-morbid mood disturbances are suspected; certainly in these cases, doses can later be increased to therapeutic antidepressant levels.[21,41]

Melatonin has been suggested useful for a number of different sleep disorders, and while it appears to reduce sleep latency and increase total sleep duration in insomnia disorder, the best evidence is for its use in circadian rhythm disturbances.[42,43]

Although not yet available for use in South Africa, orexin receptor antagonists, such as suvorexant, have been found to be effective in the treatment of insomnia.[44] Ramelteon is a selective melatonin agonist which is licensed for use in the USA. Its short-term use has been associated with some improvements in patients with insomnia disorder.[22,45]

Antihistamines are found in many over-the-counter preparations for insomnia, and there is limited evidence to support their efficacy in treating insomnia disorder.[20,46] Promethazine and hydroxyzine have been associated with inducing sleep in healthy volunteers, although these drugs have long half-lives and are associated with next-day impairment.[47]

Low doses of the atypical antipsychotics olanzapine and quetiapine have been used to treat insomnia disorder; their adverse side-effect profile limits their use as first-line agents.[48]

STEP 4: ASSESS RESPONSE TO TREATMENT

In order to determine response to medication, it is important to ask about change in those

symptoms initially targeted for treatment. This includes not only nocturnal symptoms (e.g., difficulty falling asleep, total duration of sleep), but also daytime symptoms (e.g., tiredness, difficulty concentrating), and the impact of symptoms on function. Side effects of the medication should also be determined.

Patients who are intolerant of a particular medication can, of course, be switched to another agent. For example, zolpidem, with its shorter half-life, may be associated with less daytime sleepiness than zopiclone. Similarly, substitution for a hypnotic agent by a relatively sedating antidepressant may prove useful.

Benzodiazepines appear to be most effective when administered for short periods of time and should be tapered and discontinued as soon as possible after resolution of symptoms.[49,50]

Optimise dose and duration

Benzodiazepine- and non-benzodiazepine hypnotics typically demonstrate efficacy immediately. Nevertheless, doses and the timing of doses may require some experimentation before an optimal regimen is established. As a general principle, however, doubling up on standard doses of benzodiazepines is a strategy more likely to promote adverse effects than to facilitate sleep, and doses should therefore be increased incrementally. Older patients are likely to require significantly lower doses of medication and may be more prone to adverse events.[20,51]

STEP 5 : MAINTENANCE OF TREATMENT

As noted earlier, when the patient has a good response to medication, it is important to reinforce the necessity for tapering the medication. The long-term prescription of benzodiazepines is generally discouraged.[50] It should be noted, however, that some patients do seem to require ongoing chronic treatment with hypnotic medications. Caution should similarly be employed with the newer non-benzodiazepine agents, although some studies have concluded that these can be used for longer periods of time without causing dependence.[52]

STEP 6: RE-ASSESSMENT

When insomnia does not respond to a clinical trial of optimal dose and duration, it is useful to re-assess a number of factors. The presence of certain features may impact the choice of the subsequent intervention. Polysomnography may be indicated in patients who have not responded to medication.

a. **Comorbid substance use:** In patients who fail to respond to pharmacotherapy, the possibility of comorbid substance use should

Table 10.3. Sleep centres in South Africa

Kwazulu-Natal	
Durban Sleep Centre (EEG and sleep laboratory)	(031) 268-5091
Gauteng	
Benoni Sleep Centre	(011) 422-4531
Morningside Sleep Clinic	(011) 784-0278
Garden City Sleep Centre	(011) 495-5089
Waterfall Sleep Clinic	(011) 304-7820
Pretoria Sleep Centre	(012) 343-0780
Western Cape	
Cape Sleep Centre	(021) 633-2215
Constantia Sleep Centre	(021) 761 3109
Somerset West Sleep Centre	(021) 840-7103
Greyton Sleep Centre	(028) 254-9898
Limpopo	
Polokwane Sleep Centre	(015) 291-3288

again be considered. There may be a need to withdraw the substance, as well as provide symptomatic treatment for insomnia.[28]

b. **Underlying disorder:** Patients with insomnia who fail to respond to medication should be thoroughly re-assessed for an underlying psychiatric disorder (particularly depression), medical disorder, or sleep disorder (such as breathing-related sleep disorder). Polysomnography may be a particularly useful tool here; for example, the treatment of sleep state misperception (in which there is a marked discrepancy between subjective and objective estimates of sleep) may require specific behavioural techniques.[53,54]

c. **Psychosocial issues:** Psychosocial circumstances that continue to complicate the course of insomnia need to be assessed, as these may necessitate appropriate intervention.

STEP 7: TREATMENT RESISTANCE

Many patients go on to develop symptoms of persistent insomnia (symptoms lasting for longer than three months), with 40% of this population not responding to first-line pharmacological treatments.[55] Behavioural interventions may be a particularly important treatment strategy at this time.[6,56]

After the failure of an adequate clinical trial of medication in a patient where re-assessment sheds no light on any further unresolved factors, a different agent should be used. It may be advisable to switch classes of medication. Alternatively, a combined trial with cognitive behavioural therapy may be considered.[7,9]

Referral to a specialised sleep centre may ultimately be required. Table 3 lists sleep centres by province.

ADDITIONAL READING

1. Wilson S, Anderson K, Baldwin D, *et al*. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders: An update. J Psychopharmacol (Oxf). 2019 Aug;33(8):923-47.
2. Abad VC, Guilleminault C. Insomnia in elderly patients: Recommendations for pharmacological management. Drugs Aging. 2018 Sep;35(9):791-817.
3. Heesch CB. The long-term use of sedative hypnotics in chronic insomnia. Mental Health Clinician. 2014;4(2):78-81.
4. Riemann D, Nissen C, Palagini L, *et al*. The neurobiology, investigation, and treatment of chronic insomnia. The Lancet Neurology. 2015;14(5):547-58.
5. Dassanayake T, Michie P, Carter G, *et al*. Effects of benzodiazepines, antidepressants and opioids on driving: A systematic review and meta-analysis of epidemiological and experimental evidence. Drug Saf. 2011;34(2):125-56.
6. Gunja N. In the Zzz zone: The effects of Z-drugs on human performance and driving. J Med Toxicol. 2013;9(2):163-71.
7. Baglioni C, Regen W, Teghen A, *et al*. Sleep changes in the disorder of insomnia: A meta-analysis of polysomnographic studies. Sleep Med Rev. 2014;18(3):195-213.
8. Sudak DM, Kloss J, Zamzow J. Integration of cognitive-behavioral therapy and pharmacotherapy in the treatment of insomnia. Int J Cogn Ther. 2014;7(2):162-74.

REFERENCES

1. Ford ES, Wheaton AG, Cunningham TJ, *et al*. Trends in outpatient visits for insomnia, sleep apnea, and prescriptions for sleep medications among US adults: Findings from the National Ambulatory Medical Care survey 1999-2010. Sleep. 2014;37(8):1283-93.
2. Li Y, Zhang X, Winkelman JW, *et al*. Association between insomnia symptoms and mortality: A prospective study of US men. Circulation. Vol. 129. 2014. p. 737-46.
3. Van Someren EJW. Brain mechanisms of insomnia: New perspectives on causes and consequences. Physiol Rev. 2021 Jul 1;101(3):995–1046.
4. Shahly V, Berglund PA, Coulouvrat C, *et al*. The associations of insomnia with costly workplace accidents and errors: Results from the America Insomnia Survey. Arch Gen Psychiatry. 2012;69(10):1054-63.
5. Li L, Wu C, Gan Y, *et al*. Insomnia and the risk of depression: A Meta-Analysis of Prospective Cohort Studies. BMC Psychiatry. 2016 Dec;16(1):375.
6. Trauer JM, Qian MY, Doyle JS, *et al*. Cognitive Behavioral Therapy for Chronic Insomnia: A Systematic Review and Meta-Analysis. Ann Intern Med. 2015 Aug 4;163(3):191-204.
7. Wu JQ, Appleman ER, Salazar RD, *et al*. Cognitive Behavioral Therapy for Insomnia Comorbid with Psychiatric and Medical Conditions: A Meta-Analysis. JAMA Intern Med. 2015 Sep 1;175(9):1461.
8. Rosenberg R, Citrome L, Drake CL. Advances in the treatment of chronic insomnia: A narrative review of new nonpharmacologic and pharmacologic therapies. Neuropsychiatr Dis Treat. 2021 Aug;Volume 17:2549-66.
9. Sudak DM, Kloss J, Zamzow J. Integration of cognitive-behavioral therapy and pharma-

cotherapy in the treatment of insomnia. Int J Cogn Ther. 2014;7(2):162-74.
10. Baglioni C, Bostanova Z, Bacaro V, *et al*. A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials Evaluating the Evidence Base of Melatonin, Light Exposure, Exercise, and Complementary and Alternative Medicine for Patients with Insomnia Disorder. J Clin Med. 2020 Jun 22;9(6):1949.
11. Hood HK, Rogojanski J, Moss TG. Cognitive behavioral therapy for chronic insomnia. Curr Treat Options Neurol. 2014;16:321.
12. Ophoff D, Slaats MA, Boudewyns A, *et al*. Sleep disorders during childhood: A practical review. Eur J Pediatr. 2018 May;177(5):641–8.
13. Carter JC, Wrede JE. Overview of sleep and sleep disorders in infancy and childhood. Pediatr Ann. 2017 Apr;46(4).
14. Ohayon MM, Carskadon MA, Guilleminault C, *et al*. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: Developing normative sleep values across the human lifespan. Sleep. 2004;27(7):1255-73.
15. Moraes W, Piovezan R, Poyares D, *et al*. Effects of aging on sleep structure throughout adulthood: A population-based study. Sleep Med. 2014 Apr;15(4):401-9.
16. Soehner AM, Kaplan KA, Harvey AG. Insomnia comorbid to severe psychiatric illness. Sleep Med Clin. 2013;8(3):361-71.
17. Asarnow LD, Soehner AM, Harvey AG. Circadian rhythms and psychiatric illness. Curr Opin Psychiatry. 2013 Nov;26(6):566-71.
18. Davies EA, O'Mahony MS. Adverse drug reactions in special populations – the elderly. Br J Clin Pharmacol. 2015 Oct;80(4):796-807.
19. Tampi RR, Tampi DJ. Efficacy and tolerability of Benzodiazepines for the Treatment of Behavioral and Psychological Symptoms of Dementia: A Systematic Review of Randomized Controlled Trials. Am J Alzheimers Demen. 2014;29(7):565-74.
20. Schroeck JL, Ford J, Conway EL, *et al*. Review of safety and efficacy of sleep medicines in older adults. Clin Ther. 2016 Nov;38(11):2340-72.
21. Everitt H, Baldwin DS, Stuart B, *et al*. Antidepressants for insomnia in adults. Cochrane Database Syst Rev. 2018(5):CD10753.
22. Wilson S, Anderson K, Baldwin D, *et al*. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders: An update. J Psychopharmacol (Oxf). 2019 Aug;33(8):923-47.
23. Van Geijlswijk IM, Korzilius HPLM, Smits MG. The Use of Exogenous Melatonin in Delayed Sleep Phase Disorder: A Meta-Analysis. Sleep. 2010;33(12):1605-14.
24. Kim MJ, Lee JH, Duffy JF. Circadian rhythm sleep disorders. J Clin Outcomes Manag. 2013;20(11):513-28.
25. Pavlova M. Circadian rhythm sleep-wake disorders. Contin Lifelong Learn Neurol. 2017 Aug;23(4):1051-63.
26. Qaseem A, Dallas P, Owens DK, *et al*. Diagnosis of obstructive sleep apnea in adults: A clinical practice guideline from the Am Coll Physicians Ann Intern Med. 2014;161(3):210-20.
27. Baglioni C, Regen W, Teghen A, *et al*. Sleep Changes in the Disorder of Insomnia: A Meta-Analysis of Polysomnographic Studies. Sleep Med Rev. 2014;18(3):195-213.
28. Conroy DA, Arnedt JT. Sleep and substance use disorders: An update. Curr Psychiatry Rep. 2014;16(10):487.
29. Okun ML, Ebert R, Saini B. A review of sleep-promoting medications used in pregnancy. Am J Obstet Gynecol. 2014;
30. Grigoriadis S, Graves L, Peer M, *et al*. Pregnancy and Delivery Outcomes Following Benzodiazepine Exposure: A Systematic Review and Meta-Analysis. Can J Psychiatry. 2020 Dec;65(12):821-34.
31. Wang S-H, Chen W-S, Tang S-E, *et al*. Benzodiazepines associated with acute respiratory failure in patients with obstructive sleep apnea. Front Pharmacol. 2019 Jan 7;9:1513.
32. Mason M, Cates CJ, Smith I. Effects of opioid, hypnotic and sedating medications on sleep-disordered breathing in adults with obstructive sleep apnoea. Cochrane Database Syst Rev. 2015(7):CD011090.
33. Hafizi S. Sleep and borderline personality disorder: A review. Asian J Psychiatr. 2013;6(6):452-9.
34. Park JH, An H, Jang ES, *et al*. The influence of personality and dysfunctional sleep-related cognitions on the severity of insomnia. Psychiatry Res. 2012;197(3):275–9.
35. Ripoll LH. Psychopharmacologic treatment of borderline personality disorder. Dialogues Clin Neurosci. 2013;15(2):213-24.
36. Cowdry RW, Gardner DL. Pharmacotherapy of borderline personality disorder. Alprazolam, carbamazepine, trifluoperazine, and tranylcypromine. Arch Gen Psychiatry. 1988;45(2):111-9.
37. Stranks EK, Crowe SF. The Acute Cognitive Effects of Zopiclone, Zolpidem, Zaleplon, and Eszopiclone: A Systematic Review and Meta-Analysis. J Clin Exp Neuropsychol. 2014 Aug 9;36(7):691-700.
38. Gunja N. In the Zzz zone: The effects of Z-drugs on human performance and driving. J Med Toxicol. 2013;9(2):163-71.

39. Dell'osso B, Lader M. Do benzodiazepines still deserve a major role in the treatment of psychiatric disorders? A critical reappraisal. Eur Psychiatry. 2013;28(1):7-20.
40. Jaffer KY, Chang T, Vanle B, *et al*. Trazodone for Insomnia: A Systematic Review. Innov Clin Neurosci. 2017 Aug;14(7-8):24-34.
41. Thaler KJ, Morgan LC, Van Noord M, *et al*. Comparative Effectiveness of Second-Generation Antidepressants for Accompanying Anxiety, Insomnia, and Pain in Depressed Patients: A Systematic Review. Depress Anxiety. 2012;29(6):495-505.
42. Li T, Jiang S, Han M, *et al*. Exogenous Melatonin as a Treatment for Secondary Sleep Disorders: A Systematic Review and Meta-Analysis. Front Neuroendocrinol. 2019 Jan;52:22-8.
43. Ferracioli-Oda E, Qawasmi A, Bloch MH. Meta-analysis: Melatonin for the Treatment of Primary Sleep Disorders. FOCUS. 2018 Jan;16(1):113–8.
44. Kishi T, Matsunaga S, Iwata N. Suvorexant for Primary Insomnia: A Systematic Review and Meta-Analysis of Randomized Placebo-Controlled Trials. Virgili G, editor. PLOS ONE. 2015 Aug 28;10(8):e0136910.
45. Kuriyama A, Honda M, Hayashino Y. Ramelteon for the Treatment of Insomnia In Adults: A Systematic Review and Meta-Analysis. Sleep Med. 2014 Apr;15(4):385-92.
46. Krystal AD, Richelson E, Roth T. Review of the histamine system and the clinical effects of H1 antagonists: Basis for a new model for understanding the effects of insomnia medications. Sleep Med Rev. 2013 Aug;17(4):263-72.
47. Neubauer DN. New and emerging pharmacotherapeutic approaches for insomnia. Int Rev Psychiatry. 2014 Apr;26(2):214-24.
48. Thompson W, Quay TAW, Rojas-Fernandez C, *et al*. Atypical Antipsychotics for Insomnia: A Systematic Review. Sleep Med. 2016 Jun;22:13-7.
49. Janhsen K, Roser P, Hoffmann K. The problems of long-term treatment with benzodiazepines and related substances. Dtsch Arztebl Int. 2015;112(1-2):1-7.
50. Votaw VR, Geyer R, Rieselbach MM, *et al*. The Epidemiology of Benzodiazepine Misuse: A Systematic Review. Drug Alcohol Depend. 2019 Jul;200:95–114.
51. Patel D, Steinberg J, Patel P. Insomnia in the Elderly: A Review. J Clin Sleep Med. 2018 Jun 15;14(06):1017-24.
52. Curreen M, Lidmila J. Zopiclone: Is there cause for concern in addiction services and general practice? Int J Risk Saf Med. 2014;26(4):183-9.
53. Bastien CH, Ceklic T, St-Hilaire P, *et al*. Insomnia and sleep misperception. Pathol Biol. 2014 Oct;62(5):241-51.
54. Edinger JD, Krystal AD. Subtyping primary insomnia: Is sleep state misperception a distinct clinical entity? Sleep Med Rev. 2003;7(3):203-14.
55. Riemann D, Nissen C, Palagini L, *et al*. The neurobiology, investigation, and treatment of chronic insomnia. Lancet Neurol. 2015;14(5):547–58.
56. Okajima I, Nakamura M, Nishida S, *et al*. Cognitive behavioural therapy with behavioural analysis for pharmacological treatment-resistant chronic insomnia. Psychiatry Res. 2013;210(2):515-21.

11: Schizophrenia

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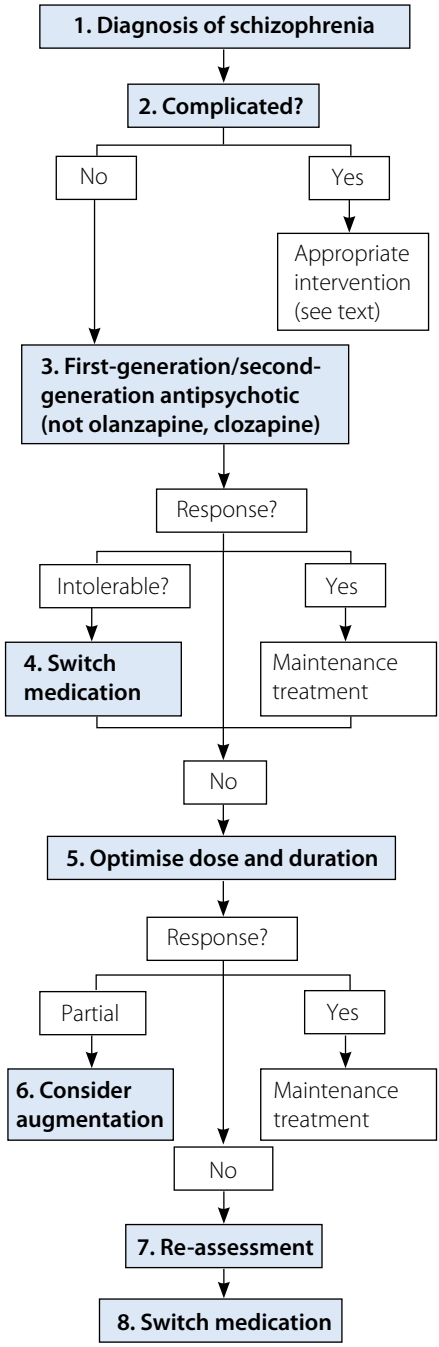
Schizophrenia is among the most distressing and disabling conditions in medicine. The introduction of the first-generation antipsychotics (FGA/typical) several decades ago led to a dramatic change in the pharmacological management of patients with schizophrenia.[1] The development of the second-generation antipsychotic (SGA/atypical) agents further contributed to the management of schizophrenia, however there may be few differences in efficacy between the two classes (with the exception of clozapine).[2-5] Advances in neuroscience and neurogenetics have, nevertheless, created some optimism about the future discovery of novel medications for the treatment of psychosis.[6]

General practitioners are frequently the first port of call in an acute psychotic episode, and may be faced with the long-term management of patients with schizophrenia after discharge from hospital.[7-9] This chapter discusses the pharmacological treatment of adult patients with an acute psychotic episode in schizophrenia, as well as some long-term management issues by way of step-by-step guidelines (see Figure 11.1.), based on the authors' review of the research literature.

Although medication is crucial in the management of schizophrenia, other treatment modalities should not be overlooked. It is well

Figure 11.1. Algorithm for pharmacotherapy of schizophrenia



known that the course of these disorders is influenced by psychological, familial, and social factors.[10,11] Psycho-education of the patient and family is a particularly important aspect of management.[12] Other psychosocial and vocational interventions, aimed at the individual and the family, are important insofar as they improve adherence, decrease stressors, improve coping strategies, and ultimately enhance prognosis.[10,11,13,14]

STEP 1: DIAGNOSIS OF SCHIZOPHRENIA

The first step in the management of schizophrenia is appropriate diagnosis and evaluation. Reliable diagnostic guidelines now exist for the diagnosis of schizophrenia (see Table 11.1.). Target symptoms for medication therapy in schizophrenia include positive symptoms (hallucinations, delusions), negative symptoms (blunting of affect, avolition), and mood symptoms. In the acute stage of a psychotic episode, the aim of pharmacotherapy is often behavioural control, while over the long term more subtle yet important symptoms, including impairments in cognitive and social function, should be targeted. Finally, with the introduction of second-generation antipsychotics for schizophrenia, targets increasingly include reduction of cardiovascular risk factors, such as cigarette smoking and obesity.[5]

Psychiatric consultation is typically advisable to rule out other psychiatric disorders characterised by psychosis (e.g., bipolar disorder, psychotic depression, brief psychotic disorder, etc). It is particularly important to rule out substance-induced psychotic disorders, as well as psychotic disorder secondary to another medical condition. Thus, patients with a first episode of a psychotic disorder deserve drug-screening, tests for syphilis, thyroid-function tests, structural brain imaging, and consideration of other tests where relevant (e.g., HIV-testing, electro-encephalography). By definition, the diagnosis of schizophrenia is made only when symptoms (including prodromal symptoms) have persisted for longer than six months. When a schizophrenia-like picture is present for less than six months, a diagnosis of schizophreniform disorder may be given, or brief psychotic episode if less than one month. However, regardless of the timing and duration of symptoms, initial medication treatment of other psychotic conditions is similar to the treatment of schizophrenia.[4,5,15-17]

STEP 2: COMPLICATIONS IN DIAGNOSIS IMPACTING PHARMACOTHERAPY

Psychotic disorders may be complicated in several ways, impacting decisions about pharmacotherapy and other interventions. In particular, an immediate consideration is

Table 11.1. Diagnostic guidelines for schizophrenia (adapted from ICD-11)

1. Two (or more) of the following, each present most of the time for a period of one month or more (or less if successfully treated). At least one of these must be (a), (b), (c), or (d): **a** Persistent delusions (e.g. grandiose, persecutory, ideas of reference) **b** Persistent hallucinations (e.g. auditory, visual) **c** Disorganised thinking (e.g. formal thought disorder, circumstantiality, tangentiality) **d** Experiences of influence, passivity or control **e** Grossly disorganised behaviour that impedes goal-directed activity **f** Psychomotor disturbance such as catatonic restlessness or agitation, posturing, negativism, stupor or mutism. **g** Negative symptoms (e.g. affective flattening, alogia, asociality, anhedonia or avolition)
2. For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning, such as work, interpersonal relations, or self-care, are markedly below the level achieved prior to the onset.
3. Schizo-affective disorder and depressive or bipolar disorder with psychotic features have been ruled out.
4. The disturbance is not due to the direct physiological effects of a substance or a general medical condition.

whether medication should be initiated in an inpatient or outpatient setting. Patients should usually be hospitalised if they:

- Pose a serious threat of harm to themselves or others.
- Cannot care for themselves or need constant supervision.
- Have a co-existing psychiatric or medical problem that would make outpatient treatment unsafe.

Regardless of whether treatment takes place on an inpatient or outpatient basis, comorbid psychiatric and medical disorder may affect medication decisions. Comorbid substance use disorders, for example, require integrated interventions if future psychotic episodes are to be prevented.[18,19] Similarly, medications used for the treatment of schizophrenia can affect comorbid medical disorders via side effects (e.g., anticholinergic effects of the antipsychotics) or via drug interactions (e.g., via cytochrome P450 system induction or inhibition).[20,21]

Antipsychotics can increase cardiovascular risk, with older agents showing pro-arrhythmic properties, whilst newer SGAs may worsen the general metabolic profile.[22] Risk for QTc prolongation may also affect antipsychotic choice as this is more common with certain agents (e.g., chlorpromazine, haloperidol) – additional risks include low potassium or magnesium levels, underlying cardiac disease, active or recent cocaine or alcohol abuse, and taking medications that prolong QTc or that inhibit metabolism of a drug that prolongs QTc.[23] A pre-treatment ECG is recommended for patients at increased cardiovascular risk.[24] Pregnancy and lactation will also affect medication decisions as antipsychotics are known to cross the placenta and enter breast milk. There is currently no evidence to suggest that either FGAs or SGAs are associated with teratogenic effects[25,26], however the second-generation antipsychotics have been associated with gestational diabetes and foetal macrosomia.[27] Single agents at lower doses are preferred, and non-pharmacological management should be explored if appropriate, however in complex situations the input of an experienced psychopharmacologist will be necessary. In general, the risk of untreated psychotic illness during pregnancy outweighs the risk of continuing or initiating antipsychotic therapy.[5]

Some features of psychotic episodes suggest that medications other than those usually employed may be useful. Catatonia may be seen in schizophrenia, mood disorders, and various medical conditions. It is known to respond to treatment with benzodiazepines or with electroconvulsive therapy (ECT).[28-30]

STEP 3: FIRST-LINE PHARMACOTHERAPY

The first-line medication management of schizophrenia relies on antipsychotics (other than olanzapine and clozapine).[5,9,31] Similar efficacy, different side-effect profiles and sometimes lower costs mean that older, "typical" antipsychotics remain a viable first-line option for some patients. Benzodiazepines may be added for the control of acute agitation.[32] Choice of medications should be influenced by anticipated side effects and tolerability; early effective intervention with a drug that is well tolerated is likely to improve adherence and offer the best chance of a favourable, long-term outcome.[4,5]

Current recommendations are to use relatively low doses of antipsychotics, particularly in first-episode schizophrenia (see also below); indeed, it is possible that some advantages of the atypical antipsychotics over the traditional agents are no longer present when low doses of the older agents are used[33], although more recent network meta-analysis suggests better efficacy with atypical antipsychotics, compared to haloperidol.[4] Clozapine is an atypical antipsychotic that runs the risk of severe side effects (myocarditis and agranulocytosis) and is therefore not used as a first-line agent.[34-37] Similarly, olanzapine should be discouraged as a first-line agent, due to the marked weight gain and metabolic complications associated with this drug.[38]

The definition of an "atypical antipsychotic" remains a subject of some debate,[39] but these agents have been suggested to differ from more typical antipsychotics in a number of respects:

- More typical antipsychotics are primarily D2 receptor blockers, while more atypical agents are not only D2 blockers, but also have a range of other effects such as 5HT2 antagonism.
- More typical antipsychotics (particularly high-potency agents) act on striatal dopaminergic pathways and are associated with extrapyramidal adverse effects, while more atypical antipsychotics act primarily on limbic and cortical dopaminergic

pathways and are associated with fewer extrapyramidal symptoms (and, as a result, probably with a lower incidence of tardive dyskinesia).[40,41]
- Both typical and atypical antipsychotics are associated with the development of cardiometabolic risk factors, although this effect appears most pronounced for some atypical antipsychotics (clozapine, olanzapine).
- More typical antipsychotics are efficacious for the positive symptoms of schizophrenia, while some more atypical agents may lead to statistically significant improvements in both positive and negative symptoms.[42-44] Partial agonists, such as aripiprazole, may be particularly useful in treating negative symptoms.[45] Some atypical antipsychotics may also be associated with less cognitive impairment, with antidepressant effects, and with improved relapse prevention.[5,18,46,47]

The older traditional antipsychotics are sometimes less expensive than the newer atypicals. Nevertheless, preliminary pharmacoeconomic studies indicate that some of the newer agents may ultimately save costs in the treatment of schizophrenia by increasing adherence and reducing hospitalisation.[48,49] After all, the cost of medication comprises only a small fraction of the cost of managing patients with schizophrenia.[50]

The traditional antipsychotics may be divided into high-potency agents (e.g., haloperidol) and low-potency agents (e.g., chlorpromazine). High-potency agents are associated with a greater incidence of extrapyramidal side effects, but with less sedation; while the low-potency agents are associated with fewer extrapyramidal side effects, but with more postural hypotension and sedation.[41,51] This is largely due to relative affinities to D2, H1, ACh, and α1 receptors.[41] The choice between these two groups therefore depends on symptoms targeted and relative importance of side effects in the particular patient. For example, sedation may be desirable in an emergency situation, but a patient with a high-functioning job may well require a high-potency agent in order to minimise this adverse effect.

STEP 4: ASSESS RESPONSE TO TREATMENT

To determine response to medication, it is important to ask about changes in those symptoms initially targeted for treatment.

Side effects of the medication should also be determined, with particular attention to those that patients may be reluctant to disclose (e.g., sexual dysfunction). Gathering collateral information from family members is often crucial in the assessment of the patient with schizophrenia.

Side effects of the antipsychotics may respond to simple interventions. For example, dystonia responds to anticholinergic agents. Most authors do not advise the routine, prolonged use of these agents due to associated cognitive dysfunction[52,53], but a short course may be useful when initiating antipsychotic agents in patients at risk (e.g., young males prescribed high-potency agents).[5,54] Akathisia may be relieved by administration of a benzodiazepine, anticholinergic medication, or ß-blocker.[55-57] Valbenazine may also prove useful for tardive dyskinesia and extrapyramidal side effects, however it is not yet available in South Africa.[58]

All patients receiving antipsychotic pharmacotherapy should receive regular metabolic monitoring (see Table 11.2.).[5,59] There is some evidence that metformin may be useful to reduce and reverse antipsychotic-related weight gain and other metabolic complications, and its use has been recommended in recent guidelines.[5,60,61]

A lower dose of medication may decrease adverse events, but runs the risk of an increase in symptoms. Untreated psychosis leads to higher rates of morbidity and mortality, therefore an adequately high dose of medication is required to achieve symptom remission. Patients with schizophrenia who are intolerant of a particular medication can, of course, be switched to another agent.[62] Switching from a high-potency to a low-potency neuroleptic or vice versa is often a useful strategy, as is switching from a typical to an atypical antipsychotic and vice versa. However, once an effective and tolerable dose is found, it is advisable to continue with this medication instead of switching agents unnecessarily. Primarily, one should treat for efficacy, and manage the side effects appropriately as they arise.

Once the patient has shown a good response to medication, it is important to reinforce the necessity for continuing the medication at the therapeutic dose despite the improvement. Guidelines for maintenance therapy of schizophrenia have become increasingly conservative, favouring longer

Table 11.2. Recommended monitoring for patients taking antipsychotics

	Baseline	1 month	2 months	3 months	6 months	Annually
Body mass index	x	x	x	x	x	x
Waist circumference	x	x	x	x	x	x
HbA1c	x			x		x
Fasting glucose(*)	x			x		x
Fasting lipids(*)	x			x		x

(*) For patients receiving olanzapine and clozapine, monitoring of these parameters should take place monthly for the first six months, and then six-monthly thereafter.

courses of medication, in view of the safety of modern agents and the likelihood of additional psychotic episodes in untreated patients with repeated past episodes.[5,19,31,63,64] While some patients may eventually be able to gradually taper medication to low doses or to stop medication without relapsing, drug holidays and intermittent treatment are not recommended.

STEP 5: OPTIMISE DOSE AND DURATION

When there is a poor response to medication, it is important to optimise dosage and duration.

What is the optimal dose and duration of antipsychotic treatment in schizophrenia? In the past, it was held that high doses of the traditional antipsychotics should be rapidly achieved. However, research indicates that most patients who fail to respond to standard doses of medication do not respond at very high doses.[4,65] While a dose range of 300-1 000 mg chlorpromazine equivalents has been recommended for acute psychotic episodes in schizophrenia[66], doses of more than 700 mg should be the exception. Lower doses than usual may be needed in first-episode psychosis and in some ethnic groups.[4,67-69] Generally, in the past, antipsychotics have been prescribed in dosages considerably higher than are required for a therapeutic effect, resulting in unnecessary adverse effects, and were thought to exert their antipsychotic action between two to four weeks; it is now clear that antipsychotics begin to have an effect almost immediately, with the first two weeks of treatment being a particularly important time to monitor for symptomatic and functional improvement.[70,71] The 2009 Schizophrenia Patient Outcomes Report Team (PORT) recommends an adequate trial lasting between two to six weeks.[10]

STEP 6: MAINTENANCE OF RESPONSE AND AUGMENTATION OF PARTIAL RESPONSE

Patients should be re-assessed at the end of a clinical trial of optimal dosage and duration. As noted earlier, when the patient has a good response to medication, it is important to reinforce the necessity for continuing the medication at the therapeutic dose despite the improvement. Guidelines for maintenance therapy of schizophrenia have become increasingly conservative, favouring longer courses of medication.

Augmenting agents may play a useful role in schizophrenia patients with comorbid symptoms/disorders.[18,72] Patients with depressive or anxiety symptoms, for example, may well benefit from the addition of an antidepressant[73], such as a TCA or SSRI, to the antipsychotic regimen, however only citalopram has shown benefit in meta-analysis for treatment of depression in schizophrenia.[74] It is particularly important to diagnose and treat depression that starts after treatment of the acute psychotic episode.[75] Augmenting atypical antipsychotics with a low dose of a traditional agent when positive symptoms persist has not been well studied, and carries an increased risk of adverse effects.[76] Systematic reviews of a range of adjunctive agents (carbamazepine, lithium, ondansetron, polyunsaturated fatty acids) in schizophrenia

are available, although results are generally disappointing and none can be recommended for routine use, although ondansetron has shown some promising results.[73,77-80]

STEP 7: RE-ASSESSMENT

When schizophrenia does not respond to a clinical trial of optimal dose and duration, it is useful to re-assess a number of factors. The presence of certain features may impact on the choice of the subsequent intervention.

a. Severity: The need for hospitalisation should be carefully monitored on a continuous basis. Clearly, patients who are a threat to themselves or others deserve to be treated on an inpatient basis. In patients with severe symptoms, consultation with a specialist is advisable. It is also critical to work with the family or significant others to ascertain the risk and develop a long-term treatment plan.

b. Adherence: It is likely that clinicians often overestimate the adherence of their patients with schizophrenia. In fact, poor adherence is perhaps the single most important cause of relapse.[81] Patients may have delusions about medication, may be too disorganised to adhere to a treatment regimen, may suffer from significant side effects, or may worry that medication is addictive or a "crutch". It is well worth checking with the patient and family whether medication is, in fact, being taken on a daily basis. For some medications, blood levels can also be measured to assess adherence.[82] Intramuscular administration of depot neuroleptics is a useful option in the non-adherent patient with schizophrenia who has had a positive previous response to oral medication[83,84] and may considerably reduce the risk of relapse.[5,85]

c. Comorbid substance use: In patients who fail to respond to pharmacotherapy, the possibility of comorbid substance use should again be considered. A structured drug-rehabilitation programme integrated with treatment of schizophrenia may be needed to help the patient to remain abstinent to prevent further psychotic episodes.[11,18]

d. Underlying medical disorder: Psychotic patients who fail to respond to medication should be thoroughly re-assessed for an underlying medical disorder.

e. Psychosocial issues: Psychosocial circumstances that continue to complicate the course of schizophrenia need to be assessed, as these may necessitate appropriate intervention.[10,11,86] It is crucial to work with the family as the patient may need help navigating psychosocial changes due to the cognitive impact of the disease process.

STEP 8: TREATMENT RESISTANCE

When a thorough re-assessment sheds no further light on the failure of a patient to respond to an adequate course of first-line treatments, alternative interventions should be considered.

There is no universally accepted definition of treatment resistance in schizophrenia, although two failed trials of adequate dose and duration of two different antipsychotics is a useful definition.[5,87,88] Referral to a psychiatrist should be considered, if not already sought. The use of medications in doses above their recommended ranges has not been shown to confer any additional benefit, and is associated with worsened side effects.[66,76,89] Dose-response studies have indicated a possible benefit from higher doses of olanzapine, although this should be carefully considered along with risk of additional side effects, particularly metabolic effects.[65] Switching from one class of medication to another may be helpful in treatment-refractory schizophrenia[90] – within the typical and atypical antipsychotics, there is a range of different classes of medication, including some agents with unique structures and mechanisms (e.g., pimozide, aripiprazole, lurasidone). The strongest evidence for the treatment of refractory schizophrenia, however, exists for clozapine, which may be particularly effective in patients who have failed several previous trials of antipsychotics.[2,3,35,36] Clozapine carries a serious risk of medical complications (including agranulocytosis, myocarditis, seizures, ileus and toxic megacolon); absorption and elimination may also be affected by age, sex, smoking status and cytochrome P450 interactions, therefore careful monitoring is necessary.[34,91-93] A subgroup of patients will demonstrate a sub-satisfactory response to clozapine, and various augmentation strategies have been attempted, with none showing particular efficacy.[94]

Non-pharmacotherapy interventions may also be considered; assertive community programmes can be useful for patients who have required multiple hospitalisations,[95-97] and electroconvulsive therapy is occasionally used in severe treatment-refractory cases.[98,99]

ADDITIONAL READING

1. American Psychiatric Association. The American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia. 3rd ed. Washington, D. C: American Psychiatric Association; 2021.
2. Zhu Y, Krause M, Huhn M, *et al*. Antipsychotic Drugs for the Acute Treatment of Patients with a First Episode of Schizophrenia: A Systematic Review with Pairwise and Network Meta-Analyses. Lancet Psychiatry. 2017 Sep;4(9):694-705.
3. Norman R, Lecomte T, Addington D, *et al*. Canadian treatment guidelines on psychosocial treatment of schizophrenia in adults. Can J Psychiatry Rev Can Psychiatr. 2017 Sep;62(9):617-23.
4. Dixon LB, Dickerson F, Bellack AS, *et al*. The 2009 schizophrenia PORT psychosocial treatment recommendations and summary statements. Schizophr Bull. 2010;36(1):48-70.
5. Emsley R, Chiliza B, Asmal L, *et al*. The nature of relapse in schizophrenia. BMC Psychiatry. 2013;13:50.
6. Correll CU, Schooler NR. Negative symptoms in schizophrenia: A review and clinical guide for recognition, assessment, and treatment. Neuropsychiatr Dis Treat. 2020 Feb 21;16:519-34.
7. Hasan A, Falkai P, Wobrock T, *et al*. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, part 1: Update 2012 on the acute treatment of schizophrenia and the management of treatment resistance. World J Biol Psychiatry. 2012;13(5):318-78.
8. Hasan A, Falkai P, Wobrock T, *et al*. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, part 2: Update 2012 on the long-term treatment of schizophrenia and management of antipsychotic-induced side effects. World J Biol Psychiatry. 2013;14(1):2-44.
9. Hasan A, Falkai P, Wobrock T, *et al*. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, part 3: Update 2015 management of special circumstances: Depression, suicidality, substance use disorders and pregnancy and lactation. World J Biol Psychiatry. 2015;16(3):142-70.
10. Leucht S, Cipriani A, Spineli L, *et al*. Comparative Efficacy and Tolerability of 15 Antipsychotic Drugs in Schizophrenia: A Multiple-Treatments Meta-Analysis. Lancet. 2013;382(9896):951-62.
11. Leucht S, Crippa A, Siafis S, *et al*. Dose-Response Meta-Analysis of Antipsychotic Drugs for Acute Schizophrenia. Am J Psychiatry. 2020 Apr 1;177(4):342-53.
12. Campana M, Falkai P, Siskind D, *et al*. Characteristics and Definitions of Ultra-Treatment-Resistant Schizophrenia - A Systematic Review and Meta-Analysis. Schizophr Res. 2021 Feb;228:218-26.
13. Musil R, Obermeier M, Russ P, *et al*. Weight gain and antipsychotics: A drug safety review. Expert Opin Drug Saf. 2015;14(1):73-96.
14. Raja M, Raja S. Clozapine safety, 40 years later. Curr Drug Saf. 2014;9(3):163-95.

REFERENCES

1. Tandon R. Antipsychotics in the treatment of schizophrenia: An overview. J Clin Psychiatry. 2011;1:4-8.
2. Asenjo Lobos C, Komossa K, Rummel-Kluge C, *et al*. Clozapine versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev. 2010(11):CD006633.
3. Essali A, Al-Haj Haasan N, Li C, *et al*. Clozapine versus typical neuroleptic medication for schizophrenia. Cochrane Database Syst Rev. 2009(1):CD000059.
4. Zhu Y, Krause M, Huhn M, *et al*. Antipsychotic Drugs for the Acute Treatment of Patients with a First Episode of Schizophrenia: A Systematic Review with Pairwise and Network Meta-Analyses. Lancet Psychiatry. 2017 Sep;4(9):694-705.
5. American Psychiatric Association. The American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia. 3rd ed. Washington, D.C.: American Psychiatric Association; 2021.
6. Trubetskoy V, Pardiñas AF, Qi T, *et al*. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. Nature. 2022 Apr;604(7906):502-8.
7. Viron M, Baggett T, Hill M, *et al*. Schizophrenia for primary care providers: How to contribute to the care of a vulnerable patient population. Am J Med. 2012;125(3):223-30.
8. Prah P, Petersen I, Nazareth I, *et al*. National changes in oral antipsychotic treatment for people with schizophrenia in primary care between 1998 and 2007 in the United Kingdom. Pharmacoepidemiol Drug Saf. 2012;21(2):161-9.
9. Addington D, Anderson E, Kelly M, *et al*. Canadian Practice Guidelines for Comprehensive Community Treatment for Schizophrenia and Schizophrenia Spectrum Disorders. Can J Psychiatry Rev Can Psychiatr. 2017 Sep;62(9):662-72.
10. Dixon LB, Dickerson F, Bellack AS, *et al*. The schizophrenia PORT psychosocial treatment recommendations and summary statements. 2009;36(1):48-70.
11. Norman R, Lecomte T, Addington D, *et al*. Canadian Treatment Guidelines on Psychosocial Treatment of Schizophrenia in Adults. Can J Psychiatry Rev Can Psychiatr. 2017 Sep;62(9):617-23.
12. Xia J, Merinder LB, Belgamwar MR. Psychoeducation for schizophrenia. Cochrane Database Syst Rev. 2011(6):CD002831.

13. Bighelli I, Rodolico A, García-Mieres H, *et al*. Psychosocial and Psychological Interventions for Relapse Prevention in Schizophrenia: A Systematic Review and Network Meta-Analysis. Lancet Psychiatry. 2021 Nov;8(11):969-80.
14. Mc Glanaghy E, Turner D, Davis GA, *et al*. A Network Meta-Analysis of Psychological Interventions for Schizophrenia and Psychosis: Impact on Symptoms. Schizophr Res. 2021 Feb;228:447-59.
15. Rebok F. Pharmacological treatment of schizoaffective disorder, schizophreniform disorder and brief psychotic disorder. Vertex. 2012;23(104):287-98.
16. Leucht S, Komossa K, Rummel-Kluge C, *et al*. A meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. Am J Psychiatry. 2009;166(2):152-63.
17. McDonagh MS, Dana T, Selph S, *et al*. Treatments for Schizophrenia in Adults: A Systematic Review. Rockville (MD): Agency for Healthcare Research and Quality (US); 2017. (AHRQ Comparative Effectiveness Reviews).
18. Hasan A, Falkai P, Wobrock T, *et al*. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, part 3: Update 2015 management of special circumstances: Depression, suicidality, substance use disorders and pregnancy and lactation. World J Biol Psychiatry. 2015;16(3):142-70.
19. Crockford D, Addington D. Canadian schizophrenia guidelines: Schizophrenia and other psychotic disorders with coexisting substance use disorders. Can J Psychiatry Rev Can Psychiatr. 2017 Sep;62(9):624-34.
20. Kennedy WK, Jann MW, Kutscher EC. Clinically significant drug interactions with atypical antipsychotics. CNS Drugs. 2013;27(12):1021-48.
21. Wijesinghe R. A review of pharmacokinetic and pharmacodynamic interactions with antipsychotics. Ment Health Clin. 2016 Jan;6(1):21-7.
22. Howell S, Yarovova E, Khwanda A, *et al*. Cardiovascular effects of psychotic illnesses and antipsychotic therapy. Heart Br Card Soc. 2019 Dec;105(24):1852-9.
23. Alvarez PA, Pahissa J. QT alterations in psychopharmacology: Proven candidates and suspects. Curr Drug Saf. 2010;5(1):97104.
24. Shah AA, Aftab A, Coverdale J. QTc prolongation with antipsychotics: Is routine ECG monitoring recommended? J Psychiatr Pr. 2014;20(3):196-206.
25. Wang Z, Brauer R, Man KKC, *et al*. Prenatal Exposure to Antipsychotic Agents and the Risk of Congenital Malformations in Children: A Systematic Review and Meta-Analysis. Br J Clin Pharmacol. 2021 Nov;87(11):4101-23.
26. Andrade C. Major congenital malformations associated with exposure to second-generation antipsychotic drugs during pregnancy. J Clin Psychiatry. 2021 Oct 5;82(5):21f14252.
27. Gentile S. Antipsychotic Therapy During Early and Late Pregnancy. A Systematic Review. Schizophr Bull. 2010;36(3):518-44.
28. Bush G, Fink M, Petrides G, *et al*. Catatonia II. Treatment with lorazepam and electroconvulsive therapy. Acta Psychiatr Scand. 1996;93(2):137-43.
29. Pelzer AC, van der Heijden FM, den Boer E. Systematic review of catatonia treatment. Neuropsychiatr Dis Treat. 2018;14:317-26.
30. Unal A, Altindag A, Demir B, *et al*. The use of lorazepam and electroconvulsive therapy in the treatment of catatonia: Treatment characteristics and outcomes in 60 patients. J ECT. 2017 Dec;33(4):290-3.
31. Barnes TRE, Schizophrenia Consensus Group of British Association for Psychopharmacology. Evidence-based guidelines for the pharmacological treatment of schizophrenia: Recommendations from the British Association for Psychopharmacology. J Psychopharmacol Oxf Engl. 2011 May;25(5):567-620.
32. Dold M, Li C, Gillies D, Leucht S. Benzodiazepine Augmentation of Antipsychotic Drugs in Schizophrenia: A Meta-Analysis and Cochrane Review of Randomized Controlled Trials. Eur Neuropsychopharmacol. 2013;23(9):102333.
33. Geddes J, Freemantle N, Harrison P, *et al*. Atypical Antipsychotics in the Treatment of Schizophrenia: Systematic Overview and Meta-Regression Analysis. BMJ. 2000;321(7273):1371-6.
34. Lundblad W, Azzam PN, Gopalan P, *et al*. Medical management of patients on clozapine: A guide for internists. J Hosp Med. 2015;
35. Samara M, Leucht S. Clozapine in treatment-resistant schizophrenia. Br J Psychiatry J Ment Sci. 2017 Apr;210(4):299.
36. Wahlbeck K, Cheine M, Essali A, *et al*. Evidence of Clozapine's Effectiveness in Schizophrenia: A Systematic Review and Meta-Analysis of Randomized Trials. Am J Psychiatry. 1999 Jul;156(7):990-9.
37. Yuen JWY, Kim DD, Procyshyn RM, *et al*. Clozapine-Induced Cardiovascular Side Effects and Autonomic Dysfunction: A Systematic Review. Front Neurosci. 2018;12:203.
38. Komossa K, Rummel-Kluge C, Hunger H, *et al*. Olanzapine versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev. 2010;(3):CD006654.
39. Leucht S, Cipriani A, Spineli L, *et al*. Comparative Efficacy and Tolerability of 15 Antipsychotic Drugs in Schizophrenia: A Multiple-Treatments Meta-Analysis. Lancet. 2013;382(9896):951-62.

40. Hartling L, Abou-Setta AM, Dursun S, *et al*. Antipsychotics in Adults with Schizophrenia: Comparative Effectiveness of First-Generation Versus Second-Generation Medications: A Systematic Review and Meta-Analysis. Ann Intern Med. 2012;157(7):498-511.
41. Stahl SM. Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. 5th ed. Cambridge University Press; 2021.
42. Fusar-Poli P, Papanastasiou E, Stahl D, *et al*. Treatments of Negative Symptoms in Schizophrenia: Meta-Analysis of 168 Randomized Placebo-Controlled Trials. Schizophr Bull. 2015 Jul 1;41(4):892-9.
43. Correll CU, Schooler NR. Negative symptoms in schizophrenia: A review and clinical guide for recognition, assessment, and treatment. Neuropsychiatr Dis Treat. 2020 Feb 21;16:519-34.
44. Krause M, Zhu Y, Huhn M, *et al*. Antipsychotic Drugs for Patients with Schizophrenia and Predominant or Prominent Negative Symptoms: A Systematic Review and Meta-Analysis. Eur Arch Psychiatry Clin Neurosci. 2018 Oct;268(7):625-39.
45. Osugo M, Whitehurst T, Shatalina E, *et al*. Dopamine Partial Agonists and Prodopaminergic Drugs for Schizophrenia: Systematic Review and Meta-Analysis of Randomized Controlled Trials. Neurosci Biobehav Rev. 2022 Apr;135:104568.
46. Hill SK, Bishop JR, Palumbo D, *et al*. Effect of second-generation antipsychotics on cognition: Current issues and future challenges. Expert Rev Neurother. 2010;10(1):43-57.
47. Kishimoto T, Agarwal V, Kishi T, *et al*. Relapse Prevention in Schizophrenia: A Systematic Review and Meta-Analysis of Second-Generation Antipsychotics Versus First-Generation Antipsychotics. Mol Psychiatry. 2013;18(1):53-66.
48. Hansen K, Lancon C, Toumi M. Pharmacoeconomic modelling in schizophrenia. Trap or support for decision makers? Eur J Health Econ. 2006;7(1):19-29.
49. Kilian R, Becker T. Impact of antipsychotic medication on the cost of schizophrenia. Expert Rev Pharmacoecon Outcomes Res. 2005;5(1):39-57.
50. Sun SX, Liu GG, Christensen DB, *et al*. Review and analysis of hospitalization costs associated with antipsychotic nonadherence in the treatment of schizophrenia in the United States. Curr Med Res Opin. 2007;23(10):2305-12.
51. Leucht C, Kitzmantel M, Chua L, *et al*. Haloperidol versus chlorpromazine for schizophrenia. Cochrane Database Syst Rev. 2008(1):CD004278.
52. Ogino S, Miyamoto S, Miyake N, *et al*. Benefits and limits of anticholinergic use in schizophrenia: Focusing on its effect on cognitive function. Psychiatry Clin Neurosci. 2014;68(1):37-49.
53. Vinogradov S, Fisher M, Warm H, *et al*. The cognitive cost of anticholinergic burden: Decreased response to cognitive training in schizophrenia. Am J Psychiatry. 2009;166(9):1055-62.
54. Buchanan RW, Kreyenbuhl J, Kelly DL, *et al*. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. Schizophr Bull. 2010 Jan;36(1):71-93.
55. Adler LA, Peselow E, Rosenthal M, *et al*. A controlled comparison of the effects of propranolol, benztropine, and placebo on akathisia: An interim analysis. Psychopharmacol Bull. 1993;29(2):283-6.
56. Lima AR, Soares-Weiser K, Bacaltchuk J, *et al*. Benzodiazepines for neuroleptic-induced acute akathisia. Cochrane Database Syst Rev. 1999(4):CD001950.
57. Pringsheim T, Gardner D, Addington D, *et al*. The assessment and treatment of antipsychotic-induced akathisia. Can J Psychiatry Rev Can Psychiatr. 2018 Nov;63(11):719-29.
58. Josiassen RC, Kane JM, Liang GS, *et al*. Long-term safety and tolerability of valbenazine (NBI-98854) in subjects with tardive dyskinesia and a diagnosis of schizophrenia or mood disorder. Psychopharmacol Bull. 2017 Aug 1;47(3):61-8.
59. Cohn TA, Sernyak MJ. Metabolic monitoring for patients treated with antipsychotic medications. Can J Psychiatry. 2006;51(8):492-501.
60. Fitzgerald I, O'Connell J, Keating D, *et al*. Metformin in the management of antipsychotic-induced weight gain in adults with psychosis: Development of the first evidence-based guideline using GRADE methodology. Evid Based Ment Health. 2022 Feb;25(1):15-22.
61. Wang Y, Wang D, Cheng J, *et al*. Efficacy and Tolerability of Pharmacological Interventions on Metabolic Disturbance Induced by Atypical Antipsychotics in Adults: A Systematic Review and Network Meta-Analysis. J Psychopharmacol Oxf Engl. 2021 Sep;35(9):1111-9.
62. Essock SM, Covell NH, Davis SM, *et al*. Effectiveness of switching antipsychotic medications. Am J Psychiatry. 2006;163(12):2090-5.
63. Emsley R, Chiliza B, Asmal L, *et al*. The nature of relapse in schizophrenia. BMC Psychiatry. 2013;13:50.
64. Galletly C, Castle D, Dark F, *et al*. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders. Aust N Z J Psychiatry. 2016 May;50(5):410-72.
65. Leucht S, Crippa A, Siafis S, *et al*. Dose-Response Meta-Analysis of Antipsychotic Drugs for Acute Schizophrenia. Am J Psychiatry. 2020 Apr 1;177(4):342-53.
66. Gardner DM, Murphy AL, O'Donnell H, *et al*. International consensus study of antipsychotic dosing. Am J Psychiatry. 2010 Jun;167(6):686-93.

67. Ormerod S, McDowell SE, Coleman JJ, *et al*. Ethnic Differences in the Risks of Adverse Reactions to Drugs Used in the Treatment of Psychoses and Depression: A Systematic Review and Meta-Analysis. Drug Saf. 2008;31(7):597-607.
68. Alvarez-Jimenez M, Parker AG, Hetrick SE, *et al*. Preventing the Second Episode: A Systematic Review and Meta-Analysis of Psychosocial and Pharmacological Trials in First-Episode Psychosis. Schizophr Bull. 2011;37(3):619-30.
69. Crossley NA, Constante M, McGuire P, *et al*. Efficacy of Atypical V. Typical Antipsychotics in the Treatment of Early Psychosis: Meta-Analysis. Br J Psychiatry. 2010;196(6):434-9.
70. Agid O, Seeman P, Kapur S. The "delayed onset" of antipsychotic action – an idea whose time has come and gone. J Psychiatry Neurosci. 2006;31(2):93-100.
71. Agid O, Kapur S, Arenovich T, *et al*. Delayed-onset hypothesis of antipsychotic action: A hypothesis tested and rejected. Arch Gen Psychiatry. 2003;60(12):1228-35.
72. Siris SG. Depression in schizophrenia: Perspective in the era of "atypical" antipsychotic agents. Am J Psychiatry. 2000;157(9):1379-89.
73. Stroup TS, Gerhard T, Crystal S, *et al*. Comparative Effectiveness of Adjunctive Psychotropic Medications in Patients with Schizophrenia. JAMA Psychiatry. 2019 May 1;76(5):508-15.
74. Gregory A, Mallikarjun P, Upthegrove R. Treatment of Depression in Schizophrenia: Systematic Review and Meta-Analysis. Br J Psychiatry J Ment Sci. 2017 Oct;211(4):198-204.
75. Hawton K, Sutton L, Haw C, *et al*. Schizophrenia and Suicide: Systematic Review of Risk Factors. Br J Psychiatry. 2005;187:9-20.
76. Canadian Agency for Drugs and Technologies in Health. Combination and High-Dose Atypical Antipsychotic Therapy in Patients with Schizophrenia: Systematic Review. CADTH Technol Overv. 2012;2(3):2301.
77. Zheng W, Cai D-B, Zhang Q-E, *et al*. Adjunctive Ondansetron for Schizophrenia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Psychiatr Res. 2019 Jun;113:27-33.
78. Leucht S, Kissling W, McGrath J. Lithium for schizophrenia. Cochrane Database Syst Rev. 2015(10):CD003834.
79. Leucht S, Helfer B, Dold M, *et al*. Carbamazepine for schizophrenia. Cochrane Database Syst Rev. 2014(5):CD001258.
80. Joy CB, Mumby-Croft R, Joy LA. Polyunsaturated fatty acid supplementation for schizophrenia. Cochrane Database Syst Rev. 2006(3):CD001257.
81. Valenstein M, Blow FC, Copeland LA, *et al*. Poor antipsychotic adherence among patients with schizophrenia: Medication and patient factors. Schizophr Bull. 2004;30(2):255-64.
82. Hiemke C, Dragicevic A, Grunder G, *et al*. Therapeutic monitoring of new antipsychotic drugs. Ther Drug Monit. 2004;26(2):156-60.
83. Kirson NY, Weiden PJ, Yermakov S, *et al*. Efficacy and effectiveness of depot versus oral antipsychotics in schizophrenia: Synthesizing results across different research designs. J Clin Psychiatry. 2013;74(6):568-75.
84. Park EJ, Amatya S, Kim MS, *et al*. Long-acting injectable formulations of antipsychotic drugs for the treatment of schizophrenia. Arch Pharm Res. 2013;36(6):651-9.
85. Leucht C, Heres S, Kane JM, *et al*. Oral Versus Depot Antipsychotic Drugs for Schizophrenia – a Critical Systematic Review and Meta-Analysis of Randomised Long-Term Trials. Schizophr Res. 2011;127(1-3):83-92.
86. De Silva MJ, Cooper S, Li HL, *et al*. Effect of Psychosocial Interventions on Social Functioning in Depression and Schizophrenia: Meta-Analysis. Br J Psychiatry. 2013;202(4):253-60.
87. Howes OD, McCutcheon R, Agid O, *et al*. Treatment-resistant schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) working group consensus guidelines on diagnosis and terminology. Am J Psychiatry. 2017 Mar 1;174(3):216-29.
88. Campana M, Falkai P, Siskind D, *et al*. Characteristics and Definitions of Ultra-Treatment-Resistant Schizophrenia – a Systematic Review and Meta-Analysis. Schizophr Res. 2021 Feb;228:218-26.
89. Royal College of Psychiatrists. Consensus statement on high-dose antipsychotic medication. Council Report; 2006.
90. Masand PS. A review of pharmacologic strategies for switching to atypical antipsychotics. Prim Care Companion J Clin Psychiatry. 2005;7(3):121-9.
91. Raja M, Raja S. Clozapine safety, 40 years later. Curr Drug Saf. Vol. 9. 2014. p. 163-95.
92. Munro J, O'Sullivan D, Andrews C, *et al*. Active monitoring of 12,760 clozapine recipients in the UK and Ireland. Beyond pharmacovigilance. Br J Psychiatry. 1999;175:576-80.
93. Albitar O, Harun SN, Zainal H, *et al*. Population Pharmacokinetics of Clozapine: A Systematic Review. BioMed Res Int. 2020;2020:9872936.
94. Wagner E, Löhrs L, Siskind D, *et al*. Clozapine Augmentation Strategies – a Systematic Meta-Review of Available Evidence. Treatment Options for Clozapine Resistance. J Psychopharmacol Oxf Engl. 2019 Apr;33(4):423-35.
95. Dieterich M, Irving CB, Park B, *et al*. Intensive case management for severe mental illness. Cochrane Database Syst Rev. 2010(10):CD007906.
96. Kisely SR, Campbell LA, O'Reilly R. Compulsory community and involuntary outpatient treatment for people with severe mental disorders. Cochrane Database Syst Rev. 2011(2):CD004408.

97. Malone D, Newron-Howes G, Simmonds S, *et al*. Community mental health teams (CMHTs) for people with severe mental illnesses and disordered personality. Cochrane Database Syst Rev. 2007(3):CD000270.
98. Sanghani SN, Petrides G, Kellner CH. Electroconvulsive therapy (ECT) in schizophrenia: A review of recent literature. Curr Opin Psychiatry. 2018 May;31(3):213-22.
99. Grover S, Sahoo S, Rabha A, *et al*. ECT in schizophrenia: A review of the evidence. Acta Neuropsychiatr. 2019 Jun;31(3):115-27.

12: Bipolar Disorder

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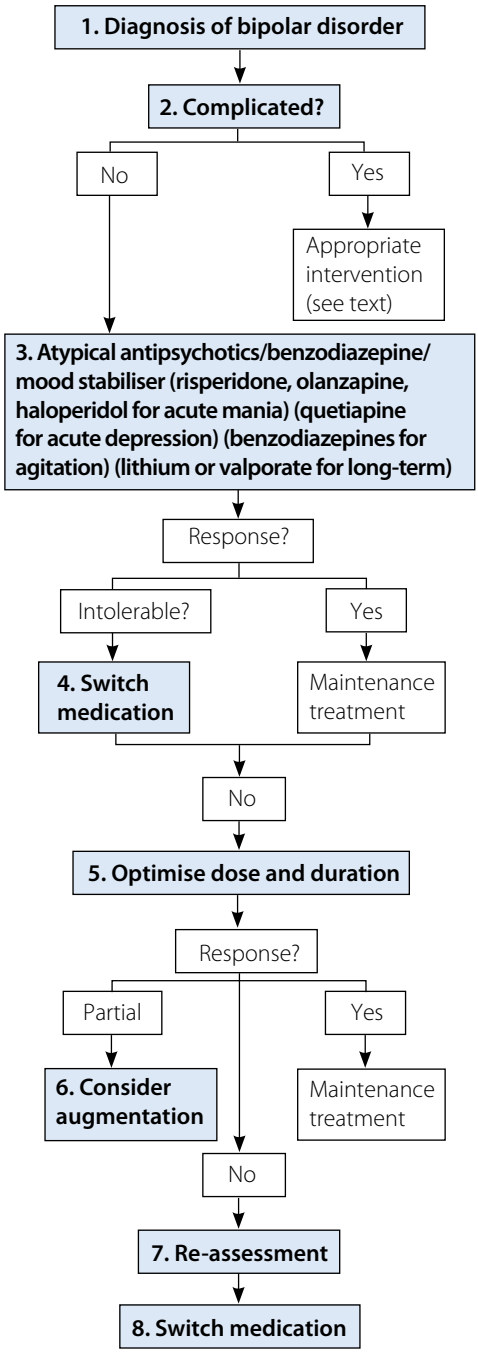
Bipolar disorder (manic depression) is a highly prevalent disorder, with substantial morbidity and mortality.[1,2] The introduction of lithium several decades ago was a major achievement in the fight to control this condition. Subsequent discoveries that certain anticonvulsant and antipsychotic agents are also effective in the treatment of bipolar disorder have increased treatment options further.[3] Primary care practitioners are frequently the first port-of-call in an acute manic or depressive episode, and are often faced with the long-term management of patients with bipolar disorder after discharge from hospital.[4] This chapter discusses the pharmacological treatment of bipolar disorder in adults, focusing on both manic and depressive episodes and maintenance therapy, and using step-by-step guidelines (see Figure 12.1.) based on the authors' review of the research literature and international guidelines.

Although medication is crucial in the management of bipolar disorder, other treatment modalities should not be overlooked. It is well known that the course of this disorder is influenced by psychological, familial, and social factors. Psycho-education of the patient and family is a particularly important aspect of management.[5,6] Other psychosocial interventions in combination with pharmacotherapy are important insofar as

Figure 12.1. Algorithm for pharmacotherapy of bipolar disorder



they increase compliance, decrease stressors, improve coping strategies, and ultimately enhance prognosis.[6] Electroconvulsive therapy (ECT) is a non-pharmacological treatment which may be considered in medical emergencies for mania and in severe presentations of bipolar disorder.[7] Its use in treatment-resistant bipolar disorder and in pregnancy is discussed later.

STEP 1: DIAGNOSIS OF BIPOLAR DISORDER

The first step in the management of bipolar disorder is appropriate diagnosis and evaluation. Reliable criteria exist for the manic and depressive episodes of bipolar disorder (see Tables 12.1., 12.2.). Targets for medication therapy in bipolar disorder include manic, hypomanic and depressive episodes. In the acute stage of a severe manic episode (which may be accompanied by psychotic features), the aim of pharmacotherapy is often behavioural control, while over the long term the focus shifts to prevention of recurrent episodes, improving psychosocial functioning, targeting residual symptoms and the management of medication-related side effects.[7,8]

Bipolar disorder is frequently misdiagnosed, and many patients will present with single or multiple episodes of depression before experiencing their first manic or hypomanic episode.[9-11] Certain aspects of the history may favour a diagnosis of bipolar depression rather than unipolar depression, namely a family history of bipolar disorder, atypical depressive features, psychotic features, earlier onset of an index depression episode and a poor response to multiple antidepressants.[12,13] In patients with mania, psychiatric consultation and often admission to hospital is advisable to manage the disorder safely and for further medical and psychiatric evaluation.

In bipolar I disorder, there is a past or current history of at least one manic episode; irrespective of the number of previous depressive episodes.

Table 12.1. Diagnostic guidelines for manic episode (adapted from ICD-11)

1. Both of the following features occurring concurrently and persisting for most of the day, nearly every day, during a period of at least 1 week, unless shortened by a treatment intervention: **A.** An extreme mood state characterized by euphoria, irritability, or expansiveness that represents a significant change from the patient's typical mood. May exhibit rapid changes among different mood states (i.e., mood lability) **B.** Increased activity or subjective experience of increased energy representing a significant change from their typical level.
2. Several of the following symptoms, representing a significant change from the patient's usual behaviour or subjective state: **A.** Inflated self-esteem or grandiosity (in psychotic mania, this may manifest as grandiose delusions) **B.** Decreased need for sleep (as distinct from insomnia where an individual wants to sleep but cannot) **C.** More talkative than usual or pressure to keep talking (a feeling of internal pressure to be more talkative) **D.** Flight of ideas or subjective experience or rapid thoughts or racing thoughts **E.** Distractibility **F.** Increase in goal-directed activity or psychomotor agitation **G.** Excessive involvement in pleasurable activities that have a high potential for painful consequences **H.** Impulsive, reckless behaviour
3. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalisation to prevent harm to self or others, or psychotic features are present.
4. The symptoms are not due to the direct physiological effects of a substance (or withdrawal) or a general medical condition.
5. The clinical presentation does not fulfil the diagnostic requirements for a mixed episode.

Table 12.2. Diagnostic guidelines for depressive episode (adapted from ICD-11)

1.	Five (or more) of the following characteristic symptoms have been present most of the day, nearly every day during a period lasting at least two weeks and represent a change from previous functioning; at least one of the symptoms is from the affective cluster. **A. Affective cluster** • Depressed mood most of the day, nearly every day, as reported or observed. This may be experienced and expressed as irritability, particularly in children or adolescents. • Markedly diminished interest or pleasure in activities, especially those normally found to be enjoyable to the individual. **B. Cognitive-behavioural cluster** • Diminished ability to think or concentrate, or indecisiveness. • Feelings of worthlessness or excessive and inappropriate guilt, which may be delusional. • Hopelessness about the future. • Recurrent thoughts of death, recurrent suicidal ideation, or evidence of suicide attempt. **C. Neurovegetative cluster** • Significantly disrupted sleep (insomnia or hypersomnia). • Significant change in appetite or weight (increase or decrease). • Psychomotor agitation or retardation. • Fatigue, loss of energy or marked tiredness following expenditure of only a minimum of effort.
2.	The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning. If function is maintained, it is only through significant additional effort.
3.	The symptoms are not due to the direct physiological effects of a substance (or withdrawal) or a general medical condition.
4.	The symptoms are not better accounted for by bereavement.
5.	The clinical presentation does not fulfil the diagnostic requirements for a mixed episode.

In bipolar II disorder, there are depressive episodes and hypomanic episodes, but no manic episodes. It has been argued that this condition is frequently misdiagnosed, as patients are unlikely to discuss hypomanic symptoms unless specifically asked about them.[14,15] Similarly, it is important to diagnose cyclothymia when patients with persistent depressive disorder (dysthymia) also have 'up' periods. Although there is less literature on this disorder, the principles of treatment for bipolar disorder may apply; including the emphasis on mood-stabilising agents (rather than on antidepressants).[16]

STEP 2: COMPLICATIONS IN DIAGNOSIS IMPACTING PHARMACOTHERAPY

Bipolar disorder may be complicated in several ways, impacting on decisions about pharmacotherapy and other interventions. In particular, an immediate consideration is whether medication should be initiated in an inpatient or outpatient setting. Patients should usually be hospitalised if they:

- Pose a serious threat of harm to themselves or others.
- Cannot care for themselves or need constant supervision
- Have a co-existing psychiatric or medical problem that would make outpatient treatment unsafe.
- Are psychotic

Whether treatment takes place on an inpatient or outpatient basis, comorbid psychiatric and medical disorders may affect medication decisions.[3] Comorbid substance-use disorders should be carefully diagnosed and will require additional interventions to complement standard therapies. Also, medications used for the treatment of bipolar disorder can affect comorbid medical disorders via side effects (e.g., the potential for metabolic syndrome with antipsychotics and valproate, hepatotoxic effects of anticonvulsants, nephrotoxic and endocrine effects of lithium) or drug interactions.[17,18]

Pregnancy and lactation will also affect medication decisions, and it is recommended that such patients receive specialist referral.[19] Use of lithium during the first trimester may be associated with a very small risk of cardiac abnormalities.[7,20] Among the anticonvulsants, both valproate and carbamazepine in the first trimester substantially increase the risk of neural tube defects and other congenital abnormalities; the risk is slightly lower with lamotrigine.[21-23]

For women receiving anticonvulsants during conception and pregnancy, daily folate to decrease the risks of neural tube defects, vitamin K in the last two months of pregnancy to prevent anticonvulsant-induced haemorrhage, serum α-fetoprotein screening, and blood-level monitoring are advisable.[24] Lithium has been discouraged by some but not all authors during breastfeeding[25], with valproate and carbamazepine considered to be safer.[26] Antipsychotics are generally considered compatible with breastfeeding, although there are concerns around possible neurodevelopmental effects associated with clozapine or chlorpromazine exposure.[26,27] Some features of manic and depressive episodes suggest that medications other than those usually employed may be useful. Catatonic symptoms in bipolar disorder, for example, may respond to treatment with benzodiazepines or ECT.[28,29]

STEP 3: FIRST-LINE PHARMACOTHERAPY

The first-line medication management of bipolar disorder may differ, depending on previous response to treatment and whether a hypomanic/manic episode or a major depressive episode is currently present.

Hypomanic/manic episode

Drugs and drug classes commonly used to treat mania include lithium, anticonvulsants, antipsychotics and benzodiazepines.[30,31]

The choice will be determined by the history of previous response, as reinstating a drug which was effective and well-tolerated is the most sensible first step, with adjunctive benzodiazepines, where necessary, to stabilise sleep patterns and reduce agitation.[32] A short-term antipsychotic agent (e.g., risperidone) may be used to aid with initial stabilisation and psychotic symptoms if present.[33] The primary medication used for long-term management, however, consists of lithium or valproate.[33]

Lithium and valproate both have efficacy in the treatment of acute mania.[34,35] There is little difference in efficacy between them, or when compared to other anticonvulsants and antipsychotics.[34,35] While there is some evidence of greater efficacy with olanzapine, given its side-effect profile, it is reserved for those patients in which lithium or valproate are poorly tolerated or unacceptable (i.e., for women of child-bearing age).

Oral loading of valproate at a dose of 20-30 mg/kg/day is safe and well tolerated, and is associated with a more rapid anti-manic effect than standard valproate and lithium titration regimens.[36] Carbamazepine also has anti-manic properties, however it is not recommended for first-line use, given the risk of serious dermatological, haematological and hepatic adverse events.[31,37] There is little to no evidence supporting the use of other anticonvulsants in the treatment of acute mania (including topiramate, lamotrigine and gabapentin).[30,38-40]

Where lithium is not an appropriate option (i.e., concerns around adherence, toxicity or tolerance) and valproate is also not favoured (i.e., in women of child-bearing age), antipsychotic medication may be considered as monotherapy.[30,33] Among the antipsychotics effective as monotherapy in acute mania, haloperidol, risperidone and olanzapine are somewhat more efficacious than aripiprazole, quetiapine and ziprasidone.[30,40] Haloperidol, a typical antipsychotic, has a more rapid onset of action than atypicals[30,31,41]; however it is usually reserved for severely behaviourally disturbed patients, as patients with bipolar disorder may be more sensitive to the neurological motor side effects of this agent.[3,42,43]

The severity of the presenting episode may also impact on pharmacotherapy. In mild-moderate manic episodes, monotherapy is recommended. In moderate-severe manic episodes (characterised by psychotic symptoms, impaired judgement, suicidal or homicidal behaviour), hospital admission is indicated, and patients will generally require treatment with a medication combination.[8,32] The combination of valproate or lithium with an atypical antipsychotic is associated with a more rapid response to treatment, as well as better response rates overall, compared to monotherapy with either agent.[7,44] In cases of severe behavioural disturbance, high-potency benzodiazepines and/or intramuscular anti-

psychotics may be a necessary measure to reduce immediate risk to self and others.[45] Combination therapy, while more efficacious than monotherapy, may be associated with a higher rate of side effects.[44]

Depressive episode

The treatment of depressive episodes in bipolar disorder is less extensively studied than the treatment of manic episodes, despite occurring more frequently.[13] Drug and drug classes commonly used to treat acute bipolar depression include SSRI antidepressants, lithium, anticonvulsants and second-generation antipsychotics.[3,33] The choice of drug will be determined by the history of previous response, as reinstating a drug which was effective and well tolerated is the most sensible first step. If there is no history of a previous episode, quetiapine is recommended as a first choice.[3,7,46] Alternative first-line strategies include other atypical antipsychotics, such as lithium, lamotrigine, valproate and fluoxetine, in combination with olanzapine.[47]

Amongst the atypical antipsychotics, quetiapine, olanzapine and lurasidone are efficacious as monotherapy.[48-50] Other second-generation antipsychotics may also be effective, although this is yet to be established. The combination of olanzapine and fluoxetine is also efficacious, however, the fixed-dose combination is not yet available in South Africa.[50,51] All antipsychotics carry an increased risk of adverse events, including marked weight gain with olanzapine and quetiapine both in the initial and maintenance phases of treatment.[47,52]

The use of SSRI antidepressants in bipolar depression is controversial; despite a favourable safety- and side-effect profile in unipolar depression, current evidence does not support the prescription of antidepressant monotherapy.[50,53] The controversy relates to the phenomenon of "switching" polarity from depression to mania, although this "switching" is also observed in patients not receiving antidepressant therapy, and is thought to be less frequent than initially reported.[53] Furthermore, there appear to be class differences: SSRIs may have lower rates of switching than SNRIs and TCAs[54]; data on other types of antidepressants are limited. Despite the concern that antidepressants may worsen the course of bipolar disorder, the combination of olanzapine and fluoxetine is efficacious in treating bipolar depression.[50,51] Indeed, if prescribed in bipolar disorder, antidepressants should always be in combination with an anti-manic agent.[3,7,32] If manic symptoms emerge during treatment with SSRIs, they should be abruptly discontinued and anti-manic treatment optimised.

The data supporting the efficacy of lithium as monotherapy in acute bipolar depression are limited[50,55], although its association with reduced suicide risk and effective anti-manic properties means it is still an appropriate first-line intervention for acute bipolar depression, especially in those with a history of severe manic episodes.[3,56]

With regard to the anticonvulsants, the evidence supporting lamotrigine as monotherapy in the acute treatment of bipolar depressive episodes is mixed.[7,50,57,58] Some evidence exists for the efficacy of valproate, although analyses are limited by a small overall sample size[3,35,59] – it has been suggested that valproate be considered in milder episodes of bipolar depression.[7]

There is growing interest in the use of ketamine as a treatment for mood disorders, particularly in treatment-resistant depression.[60,61] However, the use of ketamine as a treatment in bipolar depression still requires further research.[62] There is currently only limited evidence for the use of a single dose of intravenous ketamine as adjunctive therapy in bipolar depression.[7]

STEP 4: ASSESSING RESPONSE TO TREATMENT

In order to determine response to medication, it is important to ask about change in those symptoms initially targeted for treatment. Side effects of the medication should also be determined, with particular attention to those that patients may be reluctant to disclose (e.g., sexual dysfunction with SSRIs and antipsychotics). Gathering collateral information from family members is often crucial in the assessment response to treatment in bipolar disorder.

Side effects of the drugs used to treat bipolar mood disorder will not be discussed here in any detail. However, it may be noted that lithium use requires careful attention to fluid balance and monitoring of lithium blood levels, thyroid function, renal function, and electrocardiograms. It is necessary to monitor liver function and haematological

parameters in patients on valproate, and cardiometabolic risk factors in patients receiving valproate or antipsychotics. Problems uncovered during monitoring may respond to simple interventions (e.g., use of thyroid hormone supplementation). Patients with bipolar disorder who are intolerant of first-line medication can be switched to another first-line agent.[3]

Once the patient has shown a good response to mood stabilisers, it is important to reinforce the necessity for continuing these medications at the therapeutic dose despite this improvement.[7] Guidelines for maintenance therapy of bipolar disorder have become increasingly conservative, favouring longer courses of medication, in view of the relative safety of modern agents and the likelihood of additional episodes in untreated patients with repeated past episodes. The kindling theory of bipolar disorder suggests that repeated stopping and starting of medication, especially in the context of ongoing psychosocial stressors, may, in fact, ultimately lead to more severe and treatment-resistant episodes.[63,64] Thus, while some patients may eventually be able to gradually taper mood stabilisers to low doses or stop these medications without relapsing, drug holidays and intermittent treatment are not recommended.

STEP 5: OPTIMISE DOSE AND DURATION

When there is a poor response to medication, or when patients receiving long-term treatment for bipolar disorder experience a new manic or depressive episode, it is important to optimise dosage and duration of first-line medications. Dosage should be increased within the recommended ranges, against tolerability and side effects.

Lithium requires monitoring of blood levels to ensure that dosage is optimal. Therapeutic levels for lithium in acute mania are in the range of 0.8-1.2 mmol/L. Lithium toxicity occurs at levels greater than 1.5 mmol/L.

The role of therapeutic monitoring with valproate is less clear, with inconsistencies in the relationship between serum level and therapeutic response[65], but levels above 94 µg/ml have been associated with improved treatment response.[66] Both lithium and valproate levels should be taken 12 hours after the last dose (trough levels); and 24 hours after the last dose for extended-release formulations of valproate.

Regular monitoring of cardiometabolic risk factors is recommended for all patients receiving antipsychotic pharmacotherapy (especially patients receiving olanzapine) as these agents are associated with weight gain, and glucose and lipid dysregulation.[67] It is unclear as to what constitutes an adequate duration of trial in the treatment of bipolar episodes, although guidelines recommend up to two weeks for such a trial.[68]

STEP 6: MAINTENANCE OF RESPONSE AND AUGMENTATION OF PARTIAL RESPONSE

Patients should be re-assessed at the end of a clinical trial of optimal dosage and duration.

Partial response

Despite the number of treatment options available, many bipolar disorder patients have only a partial response despite an optimum trial of medication, and addition of a second medication may then be required. In manic episodes, atypical antipsychotic monotherapy failing to adequately control symptoms can be augmented with either valproate or lithium. Similarly, if monotherapy with lithium or valproate fails, the appropriate next step is to combine with an atypical antipsychotic.[3,41,44] Consideration should be given to the tolerability and side-effect profiles of individual drugs.[69]

For depressive episodes that only partially respond to treatment, consideration should be given to waiting a further four to six weeks for response. If this is unacceptable, quetiapine, in combination with lithium or valproate, may be associated with improvement in depressive symptoms.[7,52,70] Lamotrigine may be another choice to combine with valproate or lithium, given its efficacy in treating depressive episodes associated with bipolar disorder[58], however a more recent meta-analysis suggests it confers a higher risk of 'switching' and may be less effective than previously thought.[3,7,50,54]

Good response and maintenance

Many patients with bipolar disorder will experience multiple mood episodes throughout the course of their illness, and, as noted earlier, when the patient has a good response to mood stabilisers, it is important to reinforce the necessity for continuing these medications at the therapeutic dose despite the improvement.[71] Guidelines for

maintenance therapy of bipolar disorder have become increasingly conservative, favouring longer courses of medication. Some of the medications used in the acute treatment of bipolar disorder are effective in the prophylaxis of further episodes, although agents differ in their relative efficacy against either manic or depressive episodes.[3,7]

Lithium protects against manic and depressive episodes, and is associated with lower suicide rates and overall mortality in bipolar patients.[72,73] Lithium levels during prophylactic treatment should be in the range of 0.6 to 1.0 mEq/L; levels greater than 0.75 mmol/L provide additional protection against manic relapses.[74,75] While valproate is also effective as a maintenance drug, it may be more effective when combined with lithium.[76] The atypical antipsychotics (aripiprazole, quetiapine and olanzapine) can also be used in the maintenance and prevention of relapse, especially in the avoidance of manic episodes.[52] Some long-acting antipsychotic injectables have also been shown to be effective both as maintenance treatments in bipolar disorder and in preventing recurrence of manic episodes.[77] The long-term use of antipsychotics has been associated with metabolic syndrome, and regular physical monitoring is recommended.[78]

Quetiapine and olanzapine may additionally be effective at preventing future depressive episodes.[52,79] This also applies to lamotrigine, however this agent is less effective in preventing manic relapses.[80,81]

If antidepressant medications were used in the acute phase, they can be tapered relatively quickly after improvement of symptoms – at approximately two to four months.[3,7,54]

STEP 7: FAILURE TO RESPOND

When a manic or depressive episode of bipolar disorder does not respond to a clinical trial of optimal dose and duration, it is useful to re-assess a number of factors. The presence of certain features may impact the choice of the subsequent intervention.

a. **Severity:** The need for hospitalisation should be carefully monitored on a continuous basis. Clearly, patients who are a threat to themselves or others deserve to be treated on an inpatient basis. In addition, when severe manic or depressive symptoms are refractory to medication, the need for ECT should be considered.[7,82] In patients with severe symptoms, consultation with a specialist is advisable.

b. **Adherence:** It is likely that clinicians often overestimate the adherence of their patients with bipolar disorder. In fact, poor adherence is perhaps the single most important cause of relapse. During the 'buzz' of a hypomanic episode, patients may feel so healthy that they decide no longer to use medication. During a depressed episode, patients' negative thoughts may also generalise to decisions about medication. It is well worth checking with the patient and family whether medication is, in fact, being taken on a daily basis in a regular way. Medication blood levels can also be measured to assess adherence. Intramuscular administration of long-acting depot antipsychotics is sometimes needed for the treatment of the non-adherent patient with manic symptoms.[77,83]

c. **Comorbid substance use:** The presence of a comorbid substance-use disorder in patients with bipolar disorder is strongly associated with suicidal ideation and attempts, and should not be overlooked.[84] In patients who fail to respond to pharmacotherapy, the possibility of comorbid substance use should again be considered. A structured drug rehabilitation programme may be needed to help the patient remain abstinent to prevent further relapses.[85]

d. **Comorbid personality disorders:** Patients with bipolar disorder may also meet criteria for comorbid personality disorder, and this may result in a degree of diagnostic uncertainty.[86] In particular, mood swings in bipolar disorder may manifest in a range of maladaptive symptoms, including non-compliance with treatment. While improvement in bipolar symptoms may reduce such behaviour, there are other patients in whom these symptoms themselves should be a major target of additional treatment (i.e., psychotherapy or pharmacotherapy where indicated).[87,88]

e. **Underlying medical disorder:** Patients who fail to respond to medication should be thoroughly re-assessed for an underlying general medical disorder; medical illnesses are often underdiagnosed and undertreated in patients with bipolar disorder.[89]

f. **Psychosocial issues:** Psychosocial circumstances that continue to complicate the course of bipolar disorder need to be assessed, as these may necessitate appropriate intervention.[63]

STEP 8: TREATMENT RESISTANCE

When a thorough re-assessment sheds no further light on the failure of a patient to respond to an adequate course of first-line treatments, alternative interventions should be considered. Specialist consultation, if not already sought by this stage, is strongly recommended.

For manic episodes that do not respond to a combination of a second-generation antipsychotic and lithium/valproate, one should consider a second trial of combination treatment, replacing lithium with valproate, or vice versa. For patients who still demonstrate no response, a third combination may be necessary, using a different antipsychotic drug. Clozapine, either as monotherapy or in combination with lithium or valproate, may be effective in cases of treatment resistance,[90] however it is not licensed for this indication in most countries. ECT remains an important treatment option in refractory conditions.[82]

For depressive episodes that do not respond to antipsychotics or mood stabilisers, there are relatively few data, but it is important to bear in mind that there appears to be minimal benefit in adding an antidepressant to a mood stabiliser.[53,57] The exception to this is the combination of olanzapine and fluoxetine, which is efficacious.[51] Switching between first-line monotherapies (lithium, lamotrigine, quetiapine and valproate) and combinations with established efficacy is a reasonable approach. ECT remains an effective and safe intervention in this population, even in the presence of medical comorbidities.[82,91] Finally, ketamine (an NMDA-receptor antagonist) has recently been shown to have a rapid antidepressant action[60,61] however cannot yet be recommended as routine treatment given that there is still uncertainty around the medium- to long-term consequences.[62]

Less-well-studied augmentation strategies for the treatment of bipolar depression include: high doses of thyroxine[92], fish oil containing omega-3 fatty acids[93] and modafinil, a wakefulness-promoting agent used in the treatment of narcolepsy.[94]

ADDITIONAL READING

1. Brenner CJ, Shyn SI. Diagnosis and management of bipolar disorder in primary care: A DSM-5 update. Med Clin North Am. 2014;98(5):1025-48.
2. Cipriani A, Barbui C, Salanti G, *et al*. Comparative Efficacy and Acceptability of Antimanic Drugs in Acute Mania: A Multiple-Treatments Meta-Analysis. Lancet. 2011;378(9799):1306-15.
3. Costa Da Silva L, Alencar AP, Neto PJN, *et al*. Risk Factors for Suicide in Bipolar Disorder: A Systematic Review. J Affect Disord. 2015;170:237-54.
4. Grunze H, Vieta E, Goodwin GM, *et al*. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: Update 2012 on the long-term treatment of bipolar disorder. World J Biol Psychiatry. 2013;14(3):154-219.
5. Kohler S, Gaus S, Bschor T. The challenge of treatment in bipolar depression: Evidence from clinical guidelines, treatment recommendations and complex treatment situations. Pharmacopsychiatry. 2014;47(2):53-9.
6. McIntyre RS, Yoon J. Efficacy of antimanic treatments in mixed states. Bipolar Disord. 2012;14 Suppl 2:22-36.
7. National Institute for Health and Care Excellence. Bipolar disorder: assessment and management [Internet]. [London]: NICE; 2014 [updated 2020 Apr; cited 2016 Jun 28]. (Clinical guideline [CG185]). Available from: https://www.nice.org.uk/guidance/cg185.

REFERENCES

1. Hayes JF, Miles J, Walters K, *et al*. A Systematic Review and Meta-Analysis of Premature Mortality in Bipolar Affective Disorder. Acta Psychiatr Scand. 2015;
2. Forte A, Baldessarini RJ, Tondo L, *et al*. Longterm morbidity in bipolar-I, bipolar-II, and unipolar major depressive disorders. J Affect Disord. 2015;178:71-8.
3. Yatham LN, Kennedy SH, Parikh SV, *et al*. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord. 2018 Mar;20(2):97-170.
4. Culpepper L. The diagnosis and treatment of bipolar disorder: Decision-making in primary care. Prim Care Companion CNS Disord. 2014;16(3):26253.
5. Miklowitz DJ, Efthimiou O, Furukawa TA, *et al*. Adjunctive Psychotherapy for Bipolar Disorder: A Systematic Review and Component Network Meta-Analysis. JAMA Psychiatry. 2021 Feb 1;78(2):141-50.
6. Reinares M, Sanchez-Moreno J, Fountoulakis KN. Psychosocial interventions in bipolar disorder: What, for whom, and when. J Affect Disord. 2014;156:46-55.
7. Goodwin G, Haddad P, Ferrier I, *et al*. Evidence-based guidelines for treating bipolar disorder: Revised third edition recommendations from the

British Association for Psychopharmacology. J Psychopharmacol (Oxf). 2016 Jun;30(6):495-553.
8. Grunze H, Vieta E, Goodwin GM, *et al*. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: Update 2012 on the long-term treatment of bipolar disorder. World J Biol Psychiatry. 2013;14(3):154-219.
9. Angst J, Azorin JM, Bowden CL, *et al*. Prevalence and characteristics of undiagnosed bipolar disorders in patients with a major depressive episode: The BRIDGE study. Arch Gen Psychiatry. 2011;68(8):791-8.
10. Hu C, Xiang YT, Ungvari GS, *et al*. Undiagnosed bipolar disorder in patients treated for major depression in China. J Affect Disord. 2012;140(2):181-6.
11. Smith DJ, Griffiths E, Kelly M, *et al*. Unrecognised bipolar disorder in primary care patients with depression. Br J Psychiatry J Ment Sci. 2011 Jul;199(1):49-56.
12. Moreno C, Hasin DS, Arango C, *et al*. Depression in bipolar disorder versus major depressive disorder: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. Bipolar disord. 2012 May;14(3):271-82.
13. Hirschfeld RM. Differential diagnosis of bipolar disorder and major depressive disorder. J Affect Disord. 2014 Dec;169 Suppl 1:S12-16.
14. Calabrese J. Overview of patient care issues and treatment in bipolar spectrum and bipolar II disorder. J Clin Psychiatry. 2008;69(6):18.
15. Phillips ML, Kupfer DJ. Bipolar disorder diagnosis: challenges and future directions. The Lancet. 2013 May;381(9878):1663-71.
16. Perugi G, Hantouche E, Vannucchi G, *et al*. Cyclothymia reloaded: A reappraisal of the most misconceived affective disorder. J Affect Disord. 2015 Sep;183:119-33.
17. McLaren KD, Marangell LB. Special considerations in the treatment of patients with bipolar disorder and medical comorbidities. Ann Gen Hosp Psychiatry. 2004;3(1):7.
18. Sinha A, Shariq A, Said K, *et al*. Medical Comorbidities in Bipolar Disorder. Curr Psychiatry Rep. 2018 May;20(5):36.
19. Khan SJ, Fersh ME, Ernst C, *et al*. Bipolar disorder in pregnancy and postpartum: Principles of management. Curr Psychiatry Rep. 2016 Feb;18(2):13.
20. McKnight RF, Adida M, Budge K, *et al*. Lithium Toxicity Profile: A Systematic Review and Meta-Analysis. The Lancet. 2012 Feb;379(9817):721–8.
21. Veroniki AA, Cogo E, Rios P, *et al*. Comparative Safety of Anti-Epileptic Drugs During Pregnancy: A Systematic Review and Network Meta-Analysis of Congenital Malformations and Prenatal Outcomes. BMC Med. 2017 Dec;15(1):95.
22. Tanoshima M, Kobayashi T, Tanoshima R, *et al*. Risks of Congenital Malformations in Offspring Exposed to Valproic Acid In Utero: A Systematic Review and Cumulative Meta-Analysis. Clin Pharmacol Ther. 2015 Oct;98(4):417-41.
23. Pariente G, Leibson T, Shulman T, *et al*. Pregnancy Outcomes Following In Utero Exposure to Lamotrigine: A Systematic Review and Meta-Analysis. CNS Drugs. 2017 Jun;31(6):439-50.
24. Harden CL, Pennell PB, Koppel BS, *et al*. Management issues for women with epilepsy – focus on pregnancy (an evidence-based review): III. Vitamin K, folic acid, blood levels, and breastfeeding: Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Epilepsia. 2009;50(5):1247-55.
25. Grandjean EM, Aubry JM. Lithium: Updated human knowledge using an evidence-based approach: Part III: Clinical safety. CNS Drugs. 2009;23(5):397-418.
26. Pacchiarotti I, León-Caballero J, Murru A, *et al*. Mood stabilizers and antipsychotics during breastfeeding: Focus on bipolar disorder. Eur Neuropsychopharmacol. 2016 Oct;26(10):1562-78.
27. Parikh T, Goyal D, Scarff JR. Antipsychotic drugs and safety concerns for breast-feeding infants. South Med J. 2014;107(11):686-8.
28. Pelzer A, van der Heijden F, den Boer E. Systematic review of catatonia treatment. Neuropsychiatr Dis Treat. 2018 Jan;Volume 14:317-26.
29. Mohammadbeigi H, Alizadegan S, Barekatain M. Electroconvulsive therapy in single manic episodes: A case series. Afr J Psychiatry. 2011;14(1):56-9.
30. Cipriani A, Barbui C, Salanti G, *et al*. Comparative Efficacy and Acceptability of Antimanic Drugs in Acute Mania: A Multiple-Treatments Meta-Analysis. The Lancet. 2011 Oct;378(9799):1306-15.
31. Yildiz A, Nikodem M, Vieta E, *et al*. A network meta-analysis on comparative efficacy and all-cause discontinuation of antimanic treatments in acute bipolar mania. Psychol Med. 2015 Jan;45(2):299-317.
32. Da Silva Costa L, Alencar AP, Neto PJN, *et al*. Risk Factors for Suicide in Bipolar Disorder: A Systematic Review. J Affect Disord. 2015; 170:237-54.
33. National Department of Health, South Africa. Hospital level (Adults) Standard Treatment Guidelines and Essential Medicines List [Internet]. 5th ed. Essential Drugs Programme; 2019. Available from: https://www.knowledgehub.org.za/system/files/elibdownloads/2020-07/Hospital%20Level%20%28Adult%29%202019_v2.0.pdf

34. McKnight RF, de La Motte de Broöns de Vauvert SJGN, Chesney E, *et al*. Lithium for acute mania. Cochrane Database Syst Rev. 2019(6):CD004048.
35. Jochim J, Rifkin-Zybutz RP, Geddes J, *et al*. Valproate for acute mania. Cochrane Database Syst Rev. 2019(10):CD004052.
36. Hirschfeld RM, Baker JD, Wozniak P, *et al*. The safety and early efficacy of oral-loaded divalproex versus standard-titration divalproex, lithium, olanzapine, and placebo in the treatment of acute mania associated with bipolar disorder. J Clin Psychiatry. 2003;64(7):841-6.
37. Wang PW, Ketter TA. Clinical use of carbamazepine for bipolar disorders. Expert Opin Pharmacother. 2005;6(16):2887-902.
38. Yatham LN. Newer anticonvulsants in the treatment of bipolar disorder. J Clin Psychiatry. 2004;65(10):28-35.
39. Pigott K, Galizia I, Vasudev K, *et al*. Topiramate for acute affective episodes in bipolar disorder in adults. Cochrane Database Syst Rev. 2016(9):CD003384.
40. Kishi T, Ikuta T, Matsuda Y, *et al*. Pharmacological Treatment for Bipolar Mania: A Systematic Review and Network Meta-Analysis of Double-Blind Randomized Controlled Trials. Mol Psychiatry. 2022;27(2):1136-44.
41. Tohen M, Vieta E. Antipsychotic agents in the treatment of bipolar mania. Bipolar Disord. 2009;11(2):45-54.
42. Keck PE, McElroy SL, Strakowski SM, *et al*. Antipsychotics in the treatment of mood disorders and risk of tardive dyskinesia. J Clin Psychiatry. 2000;61 Suppl 4:33-8.
43. Gao K, Ganocy SJ, Gajwani P, *et al*. A review of sensitivity and tolerability of antipsychotics in patients with bipolar disorder or schizophrenia: Focus on somnolence. J Clin Psychiatry 69 U S. 2008;302-9.
44. Ogawa Y, Tajika A, Takeshima N, *et al*. Mood Stabilizers and Antipsychotics for Acute Mania: A Systematic Review and Meta-Analysis of Combination/Augmentation Therapy Versus Monotherapy. CNS Drugs. 2014 Nov;28(11):989-1003.
45. Correll CU, Yu X, Xiang Y, *et al*. Biological treatment of acute agitation or aggression with schizophrenia or bipolar disorder in the inpatient setting. Ann Clin Psychiatry Off J Am Acad Clin Psychiatr. 2017 May;29(2):92-107.
46. Jann MW. Diagnosis and treatment of bipolar disorders in adults: A review of the evidence on pharmacologic treatments. Am Health Drug Benefits. Vol. 7. 2014. p. 489-99.
47. Bahji A, Ermacora D, Stephenson C, *et al*. Comparative Efficacy and Tolerability of Pharmacological Treatments for the Treatment of Acute Bipolar Depression: A Systematic Review and Network Meta-Analysis. J Affect Disord. 2020 May;269:154-84.
48. Sanford M, Dhillon S. Lurasidone: A review of its use in adult patients with bipolar I depression. CNS Drugs. 2015 Mar;29(3):253-63.
49. Chiesa A, Chierzi F, De Ronchi D, *et al*. Quetiapine for Bipolar Depression: A Systematic Review and Meta-Analysis. Int Clin Psychopharmacol. 2012;27(2):76-90.
50. Taylor DM, Cornelius V, Smith L, *et al*. Comparative Efficacy and Acceptability of Drug Treatments for Bipolar Depression: A Multiple-Treatments Meta-Analysis. Acta Psychiatr Scand. 2014 Dec;130(6):452-69.
51. Silva MT, Zimmermann IR, Galvao TF, *et al*. Olanzapine Plus Fluoxetine for Bipolar Disorder: A Systematic Review and Meta-Analysis. J Affect Disord. 2013;146(3):310-8.
52. De Fruyt J, Deschepper E, Audenaert K, *et al*. Second Generation Antipsychotics in the Treatment of Bipolar Depression: A Systematic Review and Meta-Analysis. J Psychopharmacol. 2012;26(5):603-17.
53. Zhang Y, Yang H, Yang S, *et al*. Antidepressants for Bipolar Disorder: A Meta-Analysis of Randomized, Double-Blind, Controlled Trials. Neural Regen Res. 2013;8(31):2962-74.
54. Pacchiarotti I, Bond DJ, Baldessarini RJ, *et al*. The International Society for Bipolar Disorders (ISBD) Task Force Report on Antidepressant Use in Bipolar Disorders. Am J Psychiatry. 2013 Nov;170(11):1249-62.
55. Selle V, Schalkwijk S, Vazquez GH, *et al*. Treatments for acute bipolar depression: meta-analyses of placebo-controlled, monotherapy trials of anticonvulsants, lithium and antipsychotics. Pharmacopsychiatry. 2014;47(2):43-52.
56. Curran G, Ravindran A. Lithium for bipolar disorder: A review of the recent literature. Expert Rev Neurother. 2014;14(9):1079-98.
57. Solmi M, Veronese N, Zaninotto L, *et al*. Lamotrigine Compared to Placebo and Other Agents with Antidepressant Activity in Patients with Unipolar and Bipolar Depression: A Comprehensive Meta-Analysis of Efficacy and Safety Outcomes in Short-Term Trials. CNS Spectr. 2016 Oct;21(5):403-18.
58. Geddes JR, Calabrese JR, Goodwin GM. Lamotrigine for Treatment of Bipolar Depression: Independent Meta-Analysis and Meta-Regression of Individual Patient Data from Five Randomised Trials. Br J Psychiatry. 2009 Jan;194(1):4-9.
59. Bond DJ, Lam RW, Yatham LN. Divalproex Sodium Versus Placebo in the Treatment of Acute Bipolar Depression: A Systematic Review and Meta-Analysis. J Affect Disord. 2010 Aug;124(3):228-34.

60. Caddy C, Amit BH, McCloud TL, *et al*. Ketamine and other glutamate receptor modulators for depression in adults. Cochrane Database Syst Rev. 2015(9):CD011612.
61. Bahji A, Vazquez GH, Zarate CA. Comparative Efficacy of Racemic Ketamine and Esketamine for Depression: A Systematic Review and Meta-Analysis. J Affect Disord. 2021 Jan 1;278:542-55.
62. Bahji A, Zarate CA, Vazquez GH. Ketamine for Bipolar Depression: A Systematic Review. Int J Neuropsychopharmacol. 2021 Jul 23;24(7):535-41.
63. Bender RE, Alloy LB. Life stress and kindling in bipolar disorder: Review of the evidence and integration with emerging biopsychosocial theories. Clin Psychol Rev. 2011;31(3):383-98.
64. Weiss RB, Stange JP, Boland EM, *et al*. Kindling of life stress in bipolar disorder: Comparison of sensitization and autonomy models. J Abnorm Psychol. 2015 Feb;124(1):4-16.
65. Haymond J, Ensom MH. Does valproic acid warrant therapeutic drug monitoring in bipolar affective disorder? Ther Drug Monit. 2010;32(1):19-29.
66. Allen MH, Hirschfeld RM, Wozniak PJ, *et al*. Linear relationship of valproate serum concentration to response and optimal serum levels for acute mania. Am J Psychiatry. 163(2006):272-5.
67. Solmi M, Murru A, Pacchiarotti I, *et al*. Safety, tolerability, and risks associated with first- and second-generation antipsychotics: A state-of-the-art clinical review. Ther Clin Risk Manag. 2017;13:757-77.
68. Grunze H, Vieta E, Goodwin GM, *et al*. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: Update 2009 on the treatment of acute mania. World J Biol Psychiatry. 2009;10(2):85-116.
69. Maher AR, Theodore G. Summary of the comparative effectiveness review on off-label use of atypical antipsychotics. J Manag Care Pharm. 2012;1-20.
70. Sokolski KN, Denson TF. Adjunctive quetiapine in bipolar patients partially responsive to lithium or valproate. Prog Neuropsychopharmacol Biol Psychiatry. 2003;27(5):863-6.
71. Post RM, Ostacher MJ, Singh V. Controversies in the psychopharmacology of bipolar disorder. J Clin Psychiatry. 2014;75(11):30.
72. Cipriani A, Hawton K, Stockton S, *et al*. Lithium in the Prevention of Suicide in Mood Disorders: Updated Systematic Review and Meta-Analysis. BMJ. 2013;346:3646.
73. Severus E, Taylor MJ, Sauer C, *et al*. Lithium for Prevention of Mood Episodes in Bipolar Disorders: Systematic Review and Meta-Analysis. Int J Bipolar Disord. 2014;2(1):15.
74. Nolen WA, Weisler RH. The association of the effect of lithium in the maintenance treatment of bipolar disorder with lithium plasma levels: A post hoc analysis of a double-blind study comparing switching to lithium or placebo in patients who responded to quetiapine (Trial 144). Bipolar Disord. Vol. 15. 2013. p. 100–9.
75. Severus WE, Kleindienst N, Seemuller F, *et al*. What is the optimal serum lithium level in the long-term treatment of bipolar disorder – a review? Bipolar Disord. 2008;10(2):231-7.
76. Geddes JR, Goodwin GM, Rendell J, *et al*. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): A randomised open-label trial. Lancet. 2010;375(9712):385-95.
77. Pacchiarotti I, Tiihonen J, Kotzalidis GD, *et al*. Long-Acting Injectable Antipsychotics (LAIs) for Maintenance Treatment of Bipolar and Schizoaffective Disorders: A Systematic Review. Eur Neuropsychopharmacol. 2019 Apr;29(4):457-70.
78. Vancampfort D, Vansteelandt K, Correll CU, *et al*. Metabolic Syndrome and Metabolic Abnormalities in Bipolar Disorder: A Meta-Analysis of Prevalence Rates and Moderators. Am J Psychiatry. 2013;170(3):265-74.
79. Suppes T, Vieta E, Gustafsson U, *et al*. Maintenance treatment with quetiapine when combined with either lithium or divalproex in bipolar I disorder: Analysis of two large randomized, placebo-controlled trials: Research Article: Quetiapine and Lithium or Divalproex. Depress Anxiety. 2013 Nov;30(11):1089-98.
80. Smith LA, Cornelius V, Warnock A, *et al*. Effectiveness of Mood Stabilizers and Antipsychotics in the Maintenance Phase of Bipolar Disorder: A Systematic Review of Randomized Controlled Trials. Bipolar Disord. 2007;9(4):394-412.
81. Kishi T, Ikuta T, Matsuda Y, *et al*. Mood Stabilizers and/or Antipsychotics for Bipolar Disorder in the Maintenance Phase: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials. Mol Psychiatry. 2021 Aug;26(8):4146-57.
82. Sienaert P, Lambrichts L, Dols A, *et al*. Evidence-Based Treatment Strategies for Treatment-Resistant Bipolar Depression: A Systematic Review. Bipolar Disord. 2013;15(1):61-9.
83. Samalin L, Nourry A, Charpeaud T, *et al*. What is the evidence for the use of second-generation antipsychotic long-acting injectables as maintenance treatment in bipolar disorder? Nord J Psychiatry. 2014;68(4):227-35.
84. Carra G, Bartoli F, Crocamo C, *et al*. Attempted Suicide in People with Co-Occurring Bipolar and Substance Use Disorders: Systematic Review and Meta-Analysis. J Affect Disord. 2014;167:125-35.

85. Beaulieu S, Saury S, Sareen J, *et al*. The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid substance use disorders. Ann Clin Psychiatry Off J Am Acad Clin Psychiatr. 2012 Feb;24(1):38–55.
86. Ghaemi SN, Dalley S, Catania C, *et al*. Bipolar or borderline: A clinical overview. Acta Psychiatr Scand. 2014;130(2):99-108.
87. Bloom JM, Woodward EN, Susmaras T, *et al*. Use of dialectical behavior therapy in inpatient treatment of borderline personality disorder: A systematic review. Psychiatr Serv. 2012;63(9):881-8.
88. Paton C, Crawford MJ, Bhatti SF, *et al*. The use of psychotropic medication in patients with emotionally unstable personality disorder under the care of UK mental health services. J Clin Psychiatry. 2015 Apr 22;76(04):e512-8.
89. Smith DJ, Martin D, McLean G, *et al*. Multimorbidity in bipolar disorder and undertreatment of cardiovascular disease: A cross-sectional study. BMC Med. 2013;11:263.
90. Li X-B, Tang Y-L, Wang C-Y, *et al*. Clozapine for Treatment-Resistant Bipolar Disorder: A Systematic Review. Bipolar Disord. 2015 May;17(3):235-47.
91. Kellner CH, Greenberg RM, Murrough JW, *et al*. ECT in treatment-resistant depression. Am J Psychiatry. 2012;169(12):1238-44.
92. Kelly T, Lieberman DZ. The use of triiodothyronine as an augmentation agent in treatment-resistant bipolar II and bipolar disorder NOS. J Affect Disord. 2009;116(3):222-6.
93. Sarris J, Mischoulon D, Schweitzer I. Omega-3 for Bipolar Disorder: Meta-Analyses of Use in Mania and Bipolar Depression. J Clin Psychiatry. 2012;73(1):81-6.
94. Goss AJ, Kaser M, Costafreda SG, *et al*. Modafinil Augmentation Therapy in Unipolar and Bipolar Depression: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Clin Psychiatry. 2013;74(11):1101-7.

13: Alzheimer's Disease

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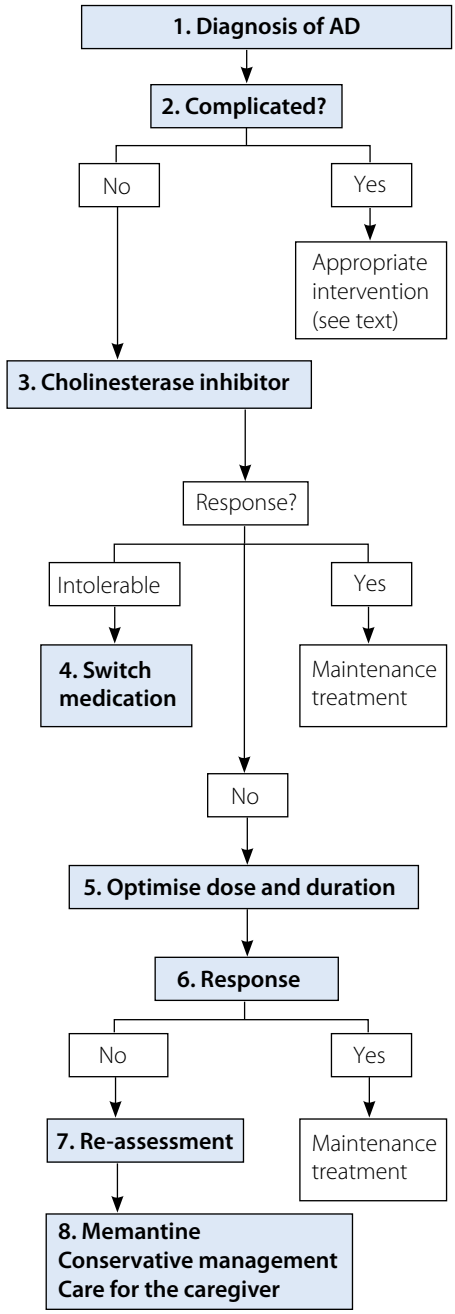
Alzheimer's disease (AD), first identified and associated with neurofibrillary tangles and plaque formation by the psychiatrist Alois Alzheimer, is the most common of the major neurocognitive disorders ("dementias") of the elderly.[1,2] Although this degenerative disorder has long been considered essentially untreatable, increased understanding of the basic neuroscience of the disorder, the recent introduction of new medications for the symptomatic treatment of AD, and the development of biomarker technologies have resulted in growing hope that more effective pharmacotherapeutic management will be found.[3-5]

A growing recognition of potential contributing causes, and knowledge of the underlying neurobiology of AD has led to a recognition of the importance of diagnosing early cognitive changes, and to the possibility of primary and secondary prevention strategies.[6,7] This area comprises a major area of interest for research, and already has important clinical implications insofar as it raises awareness of the importance of early diagnosis. Furthermore, cholinesterase inhibitors (CEIs) may also be useful in the management of other dementias, such as vascular dementia, dementia with Lewy bodies, and Parkinson's disease with dementia.[8,9]

Figure 13.1. Algorithm for pharmacotherapy of Alzheimer's disease (AD)



The management of a patient diagnosed with Alzheimer's disease requires a collaborative approach, including care-needs assessments and plans, family interventions and social and caregiver support. Carers have higher rates of depression, substance abuse, and physical illness.[10,11] It is therefore important to determine the needs of caregivers and to help meet them.

STEP 1: DIAGNOSIS OF ALZHEIMER'S DISEASE

A diagnosis of AD can only be confirmed on autopsy, on the basis of the pathognomonic tangles and plaques. Diagnosis in life remains clinical, supported by available biomarker studies and the ruling out of confounders. However, given advances in treatment, early clinical diagnosis is crucial. Fortunately, there is increasing evidence that the diagnosis of AD can reliably be made using such criteria as is found in ICD-11 or the Alzheimer's Disease criteria (see Tables 13.1., 13.2.).[12,13]

Diagnosis is made on the basis of defining criteria, and the removal of confounds. It is important to exclude potentially reversible causes of or contributors to dementia, such as syphilis, vitamin B_{12} deficiency, hypothyroidism, and normal pressure hydrocephalus.[14] Structural imaging, in addition to a thorough clinical assessment, may be a valuable tool

Table 13.1. Diagnostic guidelines for major neurocognitive disorder (adapted from ICD-11)

1. Evidence of significant cognitive decline from previous level of performance in one or more of the cognitive domains (attention/concentration, learning and memory, language, visual spatial/perceptual skills, processing speed, and executive function [e.g., problem-solving, judgement]), based on: **A.** Concern of the individual, informant or clinician; and **B.** A substantial impairment in cognitive performance (preferably documented by standardised neuropsychological testing)
2. The deficits are acquired rather than developmental
3. The deficit represents a decline from a previously attained level of functioning
4. The cognitive deficits interfere with independence in everyday activities
5. The cognitive deficits do not occur exclusively in the context of a delirium.
6. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia)

Table 13.2. Diagnostic guidelines for major neurocognitive disorder due to Alzheimer's disease s (adapted from ICD-11)

1. The criteria are met for major neurocognitive disorder (i.e., dementia).
2. Dementia presumed to be attributable to underlying Alzheimer's disease, based on quantified clinical assessment, or standardised neuropsychological/cognitive testing, neuro-imaging data, genetic testing, medical tests, family history and/or clinical history.
3. The most common form begins with neuronal impairment in the medial temporal lobes, responsible for memory formation. Early clinical history is typically characterised by: **A.** Gradual onset **B.** Progressive memory problems and word-finding difficulties **C.** Mild functional impairment
4. As Alzheimer's disease progresses and affects other brain regions, neurocognitive symptoms worsen. Atypical forms of Alzheimer's disease also characterised by progressive neurocognitive and functional impairment, with initial neurocognitive symptoms often corresponding to the brain region(s) initially affected (e.g., visual processing impairment in posterior cortical atrophy, etc.)
5. The disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance, or another mental, neurological or systemic disorder.

to support the diagnosis of AD.[15] While AD develops and progresses over time, it is convenient to consider its course in stages. Pre-syndromal disease is called mild cognitive impairment (MCI) and refers to the presence of an amnestic or non-amnestic syndrome that does not impair daily function. In mild AD, there is short-term memory impairment, which may be accompanied by symptoms of anxiety and depression. Moderate AD is characterised by worsening neuro-cognitive features, accompanying neuro-psychiatric symptoms (hallucinations, delusions, agitation, aggression), and disturbance of sleep patterns. Severe AD is characterised by prominent cognitive decline, loss of ability to perform basic activities of daily living (ADLs) and motor signs (such as rigidity).

Target symptoms of AD treatment include cognitive symptoms and impairment in daily functioning, as well as the various associated neuropsychiatric symptoms that manifest commonly during the course of the disorder.[16] Treatment should aim to maximise functional performance and quality of life, and to reduce the period of disability.

STEP 2: COMPLICATIONS IN DIAGNOSIS IMPACTING PHARMACOTHERAPY

Resolution of symptoms other than memory impairment (e.g., agitation) may be more important for caregivers than subtle improvements in memory. These neuropsychiatric symptoms of dementia (also called behavioural and psychological symptoms of dementia [BPSD]) occur frequently, and are associated with increased disability and earlier nursing-home placement.[17,18] In this section, we focus on these symptoms associated with AD, discussing the role of medications other than the cholinesterase inhibitors; however, it should be noted that the cholinesterase inhibitors may be primarily indicated for some of the neuropsychiatric symptoms and not only for memory impairment.[19,20] (See also Step 3.) The use of tools, such as the Neuropsychiatric Inventory, may guide the clinician as to the presence, extent and impact of BPSD.[21]

a. Agitation: It is important to rule out medical causes of mental status deterioration in patients with AD. For mild agitation, non-pharmacological interventions, such as environmental modifications, caregiver psycho-education and behavioural methods, may be effective.[22,23] However, a range of different medications is used for more severe agitation in Alzheimer's, perhaps most commonly low doses of neuroleptic agents. The use of all antipsychotics in patients with dementia is, however, associated with increased mortality, both in the long- and short-term, and especially with higher doses.[24,25] These effects increase with the duration of treatment.[26] A Cochrane review of haloperidol concluded that it may be useful for aggression in dementia, but that it is poorly tolerated and therefore not recommended for routine use in non-aggressive agitation.[25] As a class, the atypical antipsychotics may be effective – however the effect size is modest.[25] The effect appears most pronounced for risperidone and olanzapine although these drugs may also be associated with significant cardiovascular risk.[24,27] International guidelines suggest cautious use of atypical antipsychotics for severe agitation, at the lowest effective dose, provided the expected benefits outweigh the risks.[28] Caution should be exercised in patients with cardiovascular disease, electrolyte derangements, long QTc-interval or concomitant prescription of drugs known to lengthen QTc.[29] Long-term use of antipsychotics should be avoided – regular re-evaluation and individual risk-benefit analysis should take place, with a maximum treatment period of 12 weeks.[26] Antidepressants may also be helpful in Alzheimer's patients, although they have been less extensively studied. SSRIs (such as citalopram) and trazodone may be efficacious, and are better tolerated than antipsychotics.[30,31] The evidence for anticonvulsants and mood-stabilisers in this context (valproate, carbamazepine, topiramate, lamotrigine, lithium) is less supportive.[32,33] Benzodiazepines should generally be avoided, particularly where daily medication for agitation is needed, and, indeed, they are associated with accelerated cognitive decline.[34,35]

b. Depression: Comorbid depression is common in patients with AD in the early stages. Furthermore, in some patients, the cognitive symptoms of depression may make diagnostic differentiation from AD very difficult. In both groups of patients, a trial of antidepressants is warranted if symptoms are severe with significant

functional impairment.[36] Lower doses are needed than in younger patients. The absence of anticholinergic effects makes the selective serotonin re-uptake inhibitors a particularly useful group of agents in this context, and they may prove efficacious for a broad range of symptoms.[36] The elderly may be at increased risk of the hyponatraemia associated with drug-induced SIADH.[37]

c. **Psychosis:** Psychotic symptoms may respond well to low doses of an antipsychotic agent, although, as above, prescriptions should follow an individualised risk-benefit analysis.[24] Caution must be advised when hallucinations occur in the context of Lewy body dementia, as these patients are highly sensitive to neuroleptics.[38] Cholinesterase inhibitors have also demonstrated efficacy in the treatment of psychotic symptoms in dementia.[20] Donepezil, memantine, risperidone and aripiprazole were shown to be similarly efficacious in a recent network meta-analysis, however risperidone was less well-tolerated than the others.[20]

STEP 3: FIRST-LINE PHARMACOTHERAPY

In the algorithm (see Figure 13.1.), we suggest cholinesterase inhibitors as the first-line choice for preserving cognitive function in mild to moderate AD patients. A cholinergic hypothesis of AD was first put forward in the 1970s, and ultimately led to the development of these agents.[39,40] These agents may not only improve cognitive symptoms, but may also result in improvement in associated symptoms, including apathy, agitation, depression, and psychotic symptoms.[41,42] Some studies suggest that any one of the cholinesterase inhibitors may be used, and the choice should be made based on cost, availability and side-effect profile.[42-45] Others have suggested that donepezil is useful for all severities of cognitive impairment and is more useful than other cholinesterase inhibitors in treating patients with mild or moderate cognitive impairment.[46] A recent review also found it has a more favourable side-effect profile, compared to rivastigmine and galantamine.[47] However, they are all associated with cholinergic side effects, and it is unclear whether they delay progression of the disease process.[44,48]

A second class of molecule is available for more severe AD. The NMDA receptor antagonist memantine has been registered in Europe and the USA for more than 10 years for this indication. It has benefits for improving agitation and BPSDs, as well as slowing cognitive decline and reducing caregiver burden.[49] More recently, there have been trials to suggest that memantine may be introduced in earlier disease, together with cholinesterase inhibitors, and that together these agents may be well tolerated.[50,51] However, whilst combination cholinesterase inhibitors and memantine may improve cognition, there is insufficient evidence to suggest a clinically significant impact on ADLs and BPSDs.[52]

An immediate barrier to the use of these agents is the expense. Nevertheless, by decreasing behavioural symptoms and reducing hospitalisation and placement costs, these medications may actually be cost-effective.[53] There is the additional benefit of the possibility that caregiver burden may be considerably lightened.[54] Though not yet available in South Africa, the monoclonal anti-amyloid-β antibody, aducanumab, recently received FDA approval for treatment of Alzheimer's disease. It has shown some potential in improving cognition in patients with early Alzheimer's disease although it also has marked side effects with increasing dose.[55,56] Other amyloid-targeted therapies, including immunisation, are still being investigated as treatments for Alzheimer's disease.[3]

No good quality data exist for oestrogen replacement, vitamin E or NSAIDs in the treatment of AD.[56-59]

STEP 4: ASSESS RESPONSE TO TREATMENT

In order to determine the response to medication, it is important to set reasonable expectations for the patient's response to treatment. It may be useful to complete a scale, such as the Mini Mental Status Examination (MMSE; see Table 13.3.) or Montreal Cognitive Assessment (MOCA), in order to help quantify response to medication.[60,61]

Side effects of the medication should also be monitored. Gastro-intestinal side effects are the most common after cholinesterase inhibitors. They are dose-related and often transient, and may be particularly distressing for thin, small patients. Patients who are intolerant of a particular cholinesterase inhibitor can be switched to another.[62]

The cholinesterase inhibitors may slow the rate of decline of cognitive function and

Continued on page 140

Table 13.3. Mini-mental status examination

Orientation	**Score point**
1. What is the	
	year?.....(1)
	season?.....(1)
	month?.....(1)
	day?.....(1)
	date?.....(1)
2. Where are we?	
	Country?.....(1)
	Province?.....(1)
	Town or city?.....(1)
	Hospital?.....(1)
	Floor?.....(1)

Registration

3. Name three unrelated words, taking once second to say each. Then ask the patient to repeat all three after you have said them. Give one point for each correct answer.
Rehearse the answer (a maximum of 6 trials) until the patient learns all three.....(3)

Attention and calculation

4. Serial sevens. Give one point for each correct answer. Stop after five answers.
Alternatively: spell "world" backwards, or "herfs" (for Afrikaans-speaking patients).....(5)

Recall

5. Ask for the words learned in question 3 and above. Give one point for each correct answer.....(3)

Language

6. Point to pencil and watch. Have the patient name them as you point.....(2)

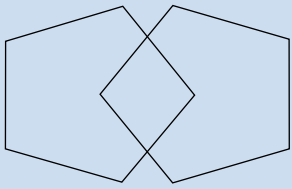
7. Have the patient follow a three-stage command: "Take this paper in your right hand, fold the paper in half, put the paper on the floor."....(3)

8. Have the patient repeat: "No ifs, ands or buts" or "Nog vis, nog vlees, nog voël" (Afrikaans-speaking patients).....(1)

9. Have the patient read and obey the following: "CLOSE YOUR EYES". (Write in large letters.).....(1)

10. Have the patient write a sentence of their choice. The sentence should contain a subject and an object, and should make sense. Ignore spelling errors when scoring.....(1)

11. Have the patient copy the design printed below. (Give one point if all the sides and angles are preserved, and if the intersecting sides form a diamond shape.).....(1)



TOTAL SCORE:.....(30)
(A score of <25 is considered abnormal)

improve activities of daily living[16,63], although individual patient response may be highly heterogeneous and independent of stage or severity of illness.[64] Improvement may be noted by caregiver reports, but also by improved or stabilised MMSE scores; this may not be noticeable during a brief trial of treatment. Therefore, a reasonable approach is a six-month trial on the recommended or maximum tolerated dose; if there is no evidence of improvement on bedside testing or from carers, the medication should be discontinued. The length of pharmacotherapy in treatment responders must be individualised, but the cholinesterase inhibitors may improve cognitive and global functioning for up to at least six months of treatment[65], and probably for longer.[66-69]

STEP 5: OPTIMISE DOSE AND DURATION

It is important to optimise the dose and duration of cholinesterase inhibitor treatment. The benefits of higher dosing are inconsistent, and may compromise drug tolerability.[63,70,71] Meta-analysis shows treatment with donepezil for 12 or 24 weeks confers a small benefit in cognitive function, activities of daily living and clinician-rated global clinical state.[63]

Donepezil is administered once daily, beginning with a dose of 5 mg at bedtime and increasing to 10 mg after four weeks (particularly in patients weighing more than 60 kg). A dose of 10 mg has been associated with better outcomes compared to 5 mg, although with slightly reduced tolerability.[63] In some cases, 15 mg may be used, where a partial and gradual treatment response is observed from 5 mg to 10 mg. Rivastigmine is initiated at 1.5 mg twice daily, and increased by 1.5 mg twice daily every two to four weeks to a maximum of 12 mg daily. If treatment is missed for more than three days, it should be restarted at the lowest daily dose and re-titrated up. Galantamine ER (extended-release) is initiated at 8 mg daily, and the dose is increased to a minimum maintenance dosage of 16 mg daily after a minimum of four weeks. Similarly, if missed for more than several days, it should be restarted at the lowest dose and titrated up to the current dose.

Caution is needed when prescribing these agents to patients with sick sinus syndrome or other supraventricular conduction defects, or when combining agents metabolised by the P450 system (donepezil, galantamine) with other medications metabolised by this pathway.[72]

STEP 6: MAINTENANCE OF TREATMENT

Re-assess the patient at the end of a clinical trial of optimal dose and duration. Data obtained at the two-year mark show that some patients are still functioning at above their expected level of deterioration when compared with untreated patients.[56,73] Unfortunately, response to the cholinesterase inhibitors is heterogeneous, so some patients do markedly better than others. Furthermore, these agents do not modify the disease process, but rather aim to delay the impact on cognitive function. While there may be some benefit to continuing therapy in patients with advanced disease[56], it has been suggested that cholinesterase medication be withdrawn once the MMSE falls to less than 12.[68] Subsequent rapid deterioration following withdrawal occasionally occurs, and would suggest that there was still some value in the therapy.[74,75]

STEP 7: RE-ASSESSMENT

Should there be no response to a clinical trial of optimal dose and duration, it may be useful to re-assess a number of factors. The diagnosis of AD should be reconsidered; in particular, other types of dementia should be excluded (although there is evidence that cholinesterase inhibitors may be useful in treating dementia due to other causes, such as Lewy body dementia or Parkinson's disease dementia).[9,76]

It is also important to reconsider the diagnosis of depression. Not only may patients with AD have comorbid depression, but depression may result in the misdiagnosis of dementia ("pseudodementia").[77] A trial of antidepressants may be the only way to exclude these possibilities.

STEP 8: TREATMENT RESISTANCE

There is evidence that if a patient does not respond to one cholinesterase inhibitor, switching to another may be useful.[62] A switch to memantine, or combination of memantine and donepezil, could also be considered, especially in moderate to severe AD.[46,51,52,78]

While development of several new pharmacotherapeutic interventions for AD

is currently under way[79,80], symptomatic management and caring for the caregiver may remain the main forms of intervention for some time. Measures to address caregiver burden, such as referral of the caregiver to an AD consumer advocacy group, may be useful.[81]

ADDITIONAL READING

1. National Institute for Health and Care Excellence. Dementia: Assessment, management and support for people living with dementia and their carers [Internet]. [London]: NICE; 2018 [cited 2022 May 11]. (NICE guideline [NG97]). Available from: https://www.nice.org.uk/guidance/ng97.
2. Rabins PV, Blacker D, Rovner BW, *et al*. American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Second edition. Am J Psychiatry. 2007;164(12 Suppl):5-56.
3. Glinz D, Gloy VL, Monsch AU, *et al*. Acetylcholinesterase Inhibitors Combined with Memantine for Moderate to Severe Alzheimer's Disease: A Meta-Analysis. Swiss medical weekly. 2019 Jun 17;149:w20093.
4. Huang YY, Shen XN, Chen SD, *et al*. Pharmacological Treatments for Psychotic Symptoms in Dementia: A Systematic Review with Pairwise and Network Meta-Analysis. Ageing Research Reviews. 2022 Jan 17:101568.
5. Kales HC, Gitlin LN, Lyketsos CG, Detroit Expert Panel on the Assessment and Management of Neuropsychiatric Symptoms of Dementia in Clinical Settings: Recommendations from a multidisciplinary expert panel. J Am Geriatr Soc. 2014;62(4):762-9.
6. Martin-Carrasco M, Ballesteros-Rodriguez J, Dominguez-Panchon AI, *et al*. Interventions for caregivers of patients with dementia. Actas Esp Psiquiatr. 2014;42(6):300-14.
7. Matsunaga S, Kishi T, Iwata N. Combination Therapy with Cholinesterase Inhibitors and Memantine for Alzheimer's Disease: A Systematic Review and Meta-Analysis. Int J Neuropsychopharmacol. 2014;18(5).
8. Gaebel W, Reed GM, Jakob R. Neurocognitive disorders in ICD-11: A new proposal and its outcome. World Psychiatry. 2019 Jun;18(2):232.
9. Cui CC, Sun Y, Wang XY, *et al*. The Effect of Anti-Dementia Drugs on Alzheimer Disease-Induced Cognitive Impairment: A Network Meta-Analysis. Medicine. 2019 Jul;98(27).
10. O'Brien JT, Holmes C, Jones M, *et al*. Clinical practice with anti-dementia drugs: A revised (third) consensus statement from the British Association for Psychopharmacology. J Psychopharmacol (Oxf). 2017 Feb;31(2):147-68.

REFERENCES

1. Prince M, Ali G-C, Guerchet M, *et al*. Recent global trends in the prevalence and incidence of dementia, and survival with dementia. Alzheimers Res Ther. 2016 Dec;8(1):23.
2. Stephan BCM, Birdi R, Tang EYH, *et al*. Secular Trends in Dementia Prevalence and Incidence Worldwide: A Systematic Review. J Alzheimers Dis JAD. 2018;66(2):653-80.
3. Jeremic D, Jiménez-Díaz L, Navarro-López JD. Past, Present and Future of Therapeutic Strategies against Amyloid-B Peptides in Alzheimer's Disease: A Systematic Review. Ageing Res Rev. 2021 Dec;72:101496.
4. Athar T, Al Balushi K, Khan SA. Recent advances on drug development and emerging therapeutic agents for Alzheimer's disease. Mol Biol Rep. 2021 Jul;48(7):5629-45.
5. Umar T, Hoda N. Alzheimer's disease: A systemic review of substantial therapeutic targets and the leading multi-functional molecules. Curr Top Med Chem. 2018 Feb 21;17(31):3370-89.
6. Vega JN, Newhouse PA. Mild cognitive impairment: Diagnosis, longitudinal course, and emerging treatments. Curr Psychiatry Rep. 2014 Oct;16(10):490.
7. Langa KM, Levine DA. The diagnosis and management of mild cognitive impairment: A clinical review. JAMA. 2014 Dec 17;312(23):2551.
8. Rolinski M, Fox C, Maidment I, *et al*. Cholinesterase inhibitors for dementia with Lewy bodies, Parkinson's disease dementia and cognitive impairment in Parkinson's disease. Cochrane Database Syst Rev. 2012(3):CD006504.
9. Wang H, Yu J, Tang S, *et al*. Efficacy and Safety of Cholinesterase Inhibitors and Memantine in Cognitive Impairment in Parkinson's Disease, Parkinson's Disease Dementia, and Dementia with Lewy Bodies: Systematic Review with Meta-Analysis and Trial Sequential Analysis. J Neurol Neurosurg Psychiatry. 2015;86(2):135-43.
10. Suehs BT, Shah SN, Davis CD, *et al*. Household members of persons with Alzheimer's disease: health conditions, healthcare resource use, and healthcare costs. J Am Geriatr Soc. 2014;62(3):435-41.
11. Pozzebon M, Douglas J, Ames D. Spouses' experience of living with a partner diagnosed with a dementia: A synthesis of the qualitative research. Int Psychogeriatr. 2016 Apr;28(4):537-56.
12. World Health Organization. ICD-11: International classification of diseases (11th revision). 11th ed. Geneva: WHO; 2019.
13. McKhann GM, Knopman DS, Chertkow H, *et al*. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for

Alzheimer's disease. Alzheimers Dement J Alzheimers Assoc. 2011 May;7(3):263-9.
14. Arvanitakis Z, Shah RC, Bennett DA. Diagnosis and management of dementia: A review. JAMA. 2019 Oct 22;322(16):1589-99.
15. Harper L, Barkhof F, Scheltens P, *et al*. An algorithmic approach to structural imaging in dementia. J Neurol Neurosurg Psychiatry. 2014;85(6):692-8.
16. Van de Glind EM, Van Enst WA, Van Munster BC, *et al*. Pharmacological treatment of dementia: A scoping review of systematic reviews. Dement Geriatr Cogn Disord. 2013;36(3–4):211-28.
17. Yu H, Wang X, He R, *et al*. Measuring the Caregiver Burden of Caring for Community-Residing People with Alzheimer's Disease. Ginsberg SD, editor. PLOS ONE. 2015 Jul 8;10(7):e0132168.
18. Wattmo C, Wallin ÅK. Early- versus late-onset Alzheimer disease: Long-term functional outcomes, nursing home placement, and risk factors for rate of progression. Dement Geriatr Cogn Disord Extra. 2017 May 4;7(1):172-87.
19. Madhusoodanan S, Ting MB. Pharmacological management of behavioral symptoms associated with dementia. World J Psychiatry. 2014;4(4):729.
20. Huang Y-Y, Teng T, Shen X-N, *et al*. Pharmacological Treatments for Psychotic Symptoms in Dementia: A Systematic Review with Pairwise and Network Meta-Analysis. Ageing Res Rev. 2022 Mar;75:101568.
21. Cummings JL, Mega M, Gray K, *et al*. The Neuropsychiatric Inventory: Comprehensive assessment of psychopathology in dementia. Neurology. 1994 Dec;44(12):2308-14.
22. Abraha I, Rimland JM, Trotta FM, *et al*. Systematic review of systematic reviews of non-pharmacological interventions to treat behavioural disturbances in older patients with dementia. The SENATOR-OnTop series. BMJ Open. 2017 Mar;7(3):e012759.
23. Dyer SM, Harrison SL, Laver K, *et al*. An overview of systematic reviews of pharmacological and non-pharmacological interventions for the treatment of behavioral and psychological symptoms of dementia. Int Psychogeriatr. 2018 Mar;30(3):295-309.
24. Yunusa I, Alsumali A, Garba AE, *et al*. Assessment of Reported Comparative Effectiveness and Safety of Atypical Antipsychotics in the Treatment of Behavioral and Psychological Symptoms of Dementia: A Network Meta-Analysis. JAMA Netw Open. 2019 Mar 22;2(3):e190828.
25. Mühlbauer V, Möhler R, Dichter MN, *et al*. Antipsychotics for agitation and psychosis in people with Alzheimer's disease and vascular dementia. Cochrane Database Syst Rev. 2021(12):CD013304.
26. Rabins PV, Rovner BW, Rummans T, *et al*. Guideline Watch (October 2014): Practice guideline for the treatment of patients with Alzheimer's disease and other dementias. FOCUS. 2017 Jan; 15(1):110-28.
27. Ballard C, Waite J. The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease. Cochrane Database Syst Rev. 2006(1):CD003476.
28. Azermai M, Petrovic M, Elseviers MM, *et al*. Systematic appraisal of dementia guidelines for the management of behavioural and psychological symptoms. Ageing Res Rev. 2012;11(1):78-86.
29. Gareri P, De Fazio P, Manfredi VG, *et al*. Use and safety of antipsychotics in behavioral disorders in elderly people with dementia. J Clin Psychopharmacol. 2014;34(1):109-23.
30. Henry G, Williamson D, Tampi RR. Efficacy and tolerability of antidepressants in the treatment of behavioral and psychological symptoms of dementia, a literature review of evidence. Am J Alzheimers Demen. 2011;26(3):169-83.
31. Seitz DP, Adunuri N, Gill SS, *et al*. Antidepressants for agitation and psychosis in dementia. Cochrane Database Syst Rev. 2011(2):CD008191.
32. Yeh YC, Ouyang WC. Mood stabilizers for the treatment of behavioral and psychological symptoms of dementia: An update review. Kaohsiung J Med Sci. 2012;28(4):185-93.
33. Lonergan E, Luxenberg J. Valproate preparations for agitation in dementia. Cochrane Database Syst Rev. 2009(3):CD003945.
34. Tampi RR, Tampi DJ. Efficacy and Tolerability of Benzodiazepines for the Treatment of Behavioral and Psychological Symptoms of Dementia: A Systematic Review of Randomized Controlled Trials. Am J Alzheimers Demen. 2014;29(7):565-74.
35. Penninkilampi R, Eslick GD. A Systematic Review and Meta-Analysis of the Risk of Dementia Associated with Benzodiazepine Use, After Controlling for Protopathic Bias. CNS Drugs. 2018 Jun;32(6):485-97.
36. Leong C. Antidepressants for depression in patients with dementia: A review of the literature. Consult Pharm. 2014;29(4):254-63.
37. Jacob S, Spinler SA. Hyponatremia associated with selective serotonin-re-uptake inhibitors in older adults. Ann Pharmacother. 2006;40(9):1618-22.
38. McKeith IG, Boeve BF, Dickson DW, *et al*. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology. 2017 Jul 4;89(1):88-100.
39. Ibach B, Haen E. Acetylcholinesterase inhibition in Alzheimer's Disease. Curr Pharm Des. 2004;10(3):231-51.

40. Saxena M, Dubey R. Target enzyme in Alzheimer's disease: Acetylcholinesterase inhibitors. Curr Top Med Chem. 2019 Apr 11;19(4):264-75.
41. Wang J, Yu J-T, Wang H-F, *et al*. Pharmacological Treatment of Neuropsychiatric Symptoms in Alzheimer's Disease: A Systematic Review and Meta-Analysis. J Neurol Neurosurg Psychiatry. 2015 Jan;86(1):101-9.
42. Tan CC, Yu JT, Wang HF, *et al*. Efficacy and Safety of Donepezil, Galantamine, Rivastigmine, and Memantine for the Treatment of Alzheimer's Disease: A Systematic Review and Meta-Analysis. J Alzheimers Dis. 2014;41(2):615-31.
43. Dou K-X, Tan M-S, Tan C-C, *et al*. Comparative Safety and Effectiveness of Cholinesterase Inhibitors and Memantine for Alzheimer's Disease: A Network Meta-Analysis of 41 Randomized Controlled Trials. Alzheimers Res Ther. 2018 Dec 27;10(1):126.
44. Matsunaga S, Fujishiro H, Takechi H. Efficacy and Safety of Cholinesterase Inhibitors for Mild Cognitive Impairment: A Systematic Review and Meta-Analysis. J Alzheimers Dis JAD. 2019 Aug 12;71(2):513-23.
45. Marucci G, Buccioni M, Ben DD, *et al*. Efficacy of acetylcholinesterase inhibitors in Alzheimer's disease. Neuropharmacology. 2021 Jun 1;190: 108352.
46. Cui C-C, Sun Y, Wang X-Y, *et al*. The Effect of Anti-Dementia Drugs on Alzheimer Disease-Induced Cognitive Impairment: A Network Meta-Analysis. Medicine (Baltimore). 2019 Jul;98(27):e16091.
47. Moreta MPG, Burgos-Alonso N, Torrecilla M, *et al*. Efficacy of acetylcholinesterase inhibitors on cognitive function in Alzheimer's disease. Review of Reviews. Biomedicines. 2021 Nov 15;9(11):1689.
48. Zhang X, Lian S, Zhang Y, *et al*. Efficacy and Safety of Donepezil for Mild Cognitive Impairment: A Systematic Review and Meta-Analysis. Clin Neurol Neurosurg. 2022 Feb;213:107134.
49. McShane R, Westby MJ, Roberts E, *et al*. Memantine for dementia. Cochrane Database Syst Rev. 2019(3):CD003154.
50. Kishi T, Matsunaga S, Oya K, *et al*. Memantine for Alzheimer's Disease: An Updated Systematic Review and Meta-Analysis. J Alzheimers Dis. 2017 Sep 18;60(2):401-25.
51. Veroniki AA, Ashoor HM, Rios P, *et al*. Comparative Safety and Efficacy of Cognitive Enhancers for Alzheimer's Dementia: A Systematic Review with Individual Patient Data Network Meta-Analysis. BMJ Open. 2022 Apr 26;12(4):e053012.
52. Glinz D, Gloy VL, Monsch AU, *et al*. Acetylcholinesterase Inhibitors Combined with Memantine for Moderate to Severe Alzheimer's disease: A Meta-Analysis. Swiss Med Wkly. 2019 Jun 17;149:w20093.
53. Hyde C, Peters J, Bond M, *et al*. Evolution of the Evidence on the Effectiveness and Cost-Effectiveness of Acetylcholinesterase Inhibitors and Memantine for Alzheimer's Disease: Systematic Review and Economic Model†. Age Ageing. 2013 Jan;42(1):14-20.
54. Masterman DL. Role of cholinesterase inhibitors in managing behavioral problems in Alzheimer's disease. Prim Care Companion J Clin Psychiatry. 2004 Jun 1;06(03):126-31.
55. Mo J-J, Li J, Yang Z, *et al*. Efficacy and Safety of Anti-Amyloid-B Immunotherapy for Alzheimer's Disease: A Systematic Review and Network Meta-Analysis. Ann Clin Transl Neurol. 2017 Dec;4(12):931-42.
56. O'Brien JT, Holmes C, Jones M, *et al*. Clinical practice with anti-dementia drugs: A revised (third) consensus statement from the British Association for Psychopharmacology. J Psychopharmacol (Oxf). 2017 Feb;31(2):147-68.
57. Maki PM, Henderson VW. Hormone therapy, dementia, and cognition: The Women's Health Initiative 10 years on. Climacteric. 2012;15(3):256-62.
58. Farina N, Isaac MG, Clark AR, *et al*. Vitamin E for Alzheimer's dementia and mild cognitive impairment. Cochrane Database Syst Rev. 2012(11):CD002854.
59. Wang J, Tan L, Wang HF, *et al*. Anti-Inflammatory Drugs and Risk of Alzheimer's Disease: An Updated Systematic Review and Meta-Analysis. J Alzheimers Dis. 2015;44(2):385-96.
60. Sheehan B. Assessment scales in dementia. Ther Adv Neurol Disord. 2012;5(6):349-58.
61. Tang-Wai DF, Smith EE, Bruneau M-A, *et al*. CCCDTD5 recommendations on early and timely assessment of neurocognitive disorders using cognitive, behavioral, and functional scales. Alzheimers Dement N Y N. 2020;6(1):e12057.
62. Blesa R, Toriyama K, Ueda K, *et al*. Strategies for continued successful treatment in patients with Alzheimer's disease: An overview of switching between pharmacological agents. Curr Alzheimer Res. 2018 Aug 15;15(10):964-74.
63. Birks JS, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. Cochrane Database Syst Rev. 2018(6):CD001190.
64. Di Santo SG, Prinelli F, Adorni F, *et al*. A meta-analysis of the efficacy of donepezil, rivastigmine, galantamine, and memantine in relation to severity of Alzheimer's disease. J Alzheimers Dis. 2013;35(2):349-61.
65. Knight R, Khondoker M, Magill N, *et al*. A Systematic Review and Meta-Analysis of the Effectiveness of Acetylcholinesterase Inhibitors and Memantine in Treating the Cognitive Symptoms of Dementia. Dement Geriatr Cogn Disord. 2018;45(3-4):131-51.

66. Xu H, Garcia-Ptacek S, Jönsson L, *et al*. Long-term effects of cholinesterase inhibitors on cognitive decline and mortality. Neurology. 2021 Apr 27;96(17):e2220-30.
67. Raskind MA, Peskind ER, Truyen L, *et al*. The cognitive benefits of galantamine are sustained for at least 36 months: A long-term extension trial. Arch Neurol. 2004 Feb;61(2):252-6.
68. National Institute for Health and Care Excellence. Dementia: Assessment, management and support for people living with dementia and their carers [Internet]. [London]: NICE; 2018 [cited 2022 May 11]. (NICE guideline [NG97]). Available from: https://www.nice.org.uk/guidance/ng97.
69. Parsons C, Lim WY, Loy C, *et al*. Withdrawal or continuation of cholinesterase inhibitors or memantine or both, in people with dementia. Cochrane Database Syst Rev. 2021(2):CD009081.
70. Loy C, Schneider L. Galantamine for Alzheimer's disease and mild cognitive impairment. Cochrane Database Syst Rev. 2006(1):CD001747.
71. Birks JS, Chong LY, Grimley Evans J. Rivastigmine for Alzheimer's disease. Cochrane Database Syst Rev. 2015(9):CD001191.
72. Trenaman SC, Bowles SK, Andrew MK, *et al*. The role of sex, age and genetic polymorphisms of CYP enzymes on the pharmacokinetics of anticholinergic drugs. Pharmacol Res Perspect. 2021 May;9(3).
73. Schneider LS, Mangialasche F, Andreasen N, *et al*. Clinical trials and late-stage drug development for Alzheimer's disease: An appraisal from 1984 to 2014. J Intern Med. 2014;275(3):251-83.
74. Rainer M, Mucke HA, Kruger-Rainer C, *et al*. Cognitive relapse after discontinuation of drug therapy in Alzheimer's disease: Cholinesterase inhibitors versus nootropics. J Neural Transm. 2001;108(11):1327-33.
75. Kim LD, Factora RM. Alzheimer dementia: Starting, stopping drug therapy. Cleve Clin J Med. 2018 Mar;85(3):209-14.
76. Matsunaga S, Kishi T, Yasue I, *et al*. Cholinesterase Inhibitors for Lewy Body Disorders: A Meta-Analysis. Int J Neuropsychopharmacol. 2016 Feb;19(2):pyv086.
77. Kang H, Zhao F, You L, *et al*. Pseudo-dementia: A neuropsychological review. Ann Indian Acad Neurol. 2014;17(2):147-54.
78. Wilkinson D, Wirth Y, Goebel C. Memantine in Patients with Moderate to Severe Alzheimer's Disease: Meta-Analyses Using Realistic Definitions of Response. Dement Geriatr Cogn Disord. 2014;37(1-2):71-85.
79. Geldenhuys WJ, Darvesh AS. Pharmacotherapy of Alzheimer's disease: current and future trends. Expert Rev Neurother. 2015;15(1):3-5.
80. Guzior N, Wieckowska A, Panek D, *et al*. Recent development of multifunctional agents as potential drug candidates for the treatment of Alzheimer's disease. Curr Med Chem. 2015;22(3):373-404.
81. McCabe M, You E, Tatangelo G. Hearing Their Voice: A Systematic Review of Dementia Family Caregivers' Needs. The Gerontologist. 2016 Oct;56(5):e70-88.

14: Attention Deficit/ Hyperactivity Disorder

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Attention deficit/hyperactivity disorder (ADHD) is characterised by symptoms of inattention and/or hyperactivity/impulsivity (see Table 14.1.). The disorder is understood to be highly prevalent (up to 5% of children and adolescents and 2.5% of adults) and associated with significant morbidity and functional impairment.[1-3] An improved understanding of the neurobiological basis of this disorder has led to significant developments in various pharmacotherapies, although the potential for adverse events should necessitate cautious prescribing.[4]

ADHD, its diagnosis and pharmacological management have frequently been the subject of intense public debate – concerns have been raised about the possibility of over-diagnosis, and risk related to subsequent over-medication.[5] Additionally, many of the first-line medications used to treat ADHD carry the potential for abuse and diversion.[6] While over-diagnosis in some settings may occur, untreated ADHD can have serious consequences (e.g., unemployment, substance abuse, poorer academic outcomes and involvement in criminal activity[7]); under-treatment is therefore an important public health concern.

Throughout this volume we have noted that both pharmacotherapy and psychotherapy have a role in the treatment of psychiatric disorders. The Multimodal Treatment Study of Children with ADHD (MTA) found that pharmacotherapy was superior to behaviour therapy for core ADHD symptoms, but that

Continued on page 147

Figure 14.1. Algorithm for pharmacotherapy of attention-deficit/ hyperactivity disorder (ADHD)

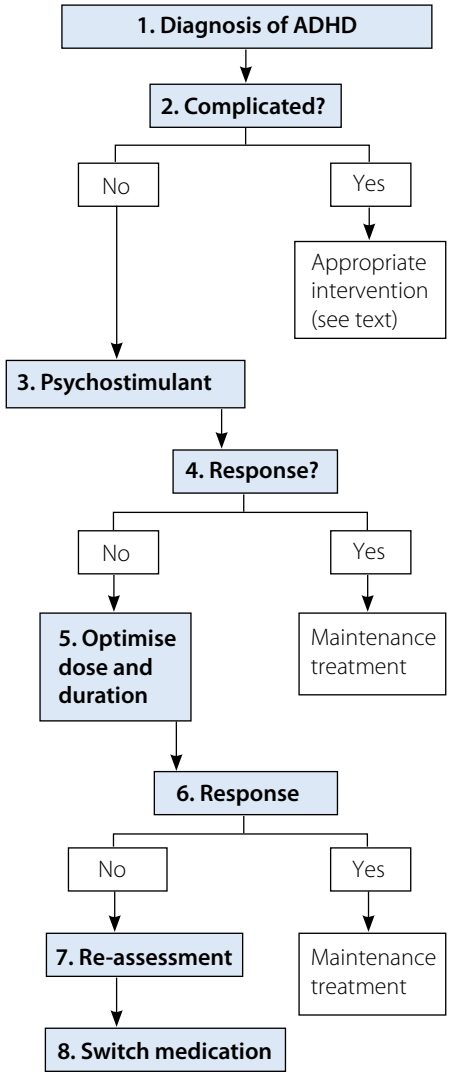

Table 14.1. Guidelines for attention-deficit/hyperactivity disorder (adapted from ICD-11)

1. Persistent pattern (e.g., for at least 6 months) of inattention and/or hyperactivity-impulsivity that is outside the limits of normal variation expected for age and level of intellectual development, as characterised by (I.) and/or (II.):

I. Inattention: Several of the following symptoms that are persistent and sufficiently severe to have a negative impact on academic, occupational or social functioning:

- **a** Difficulty sustaining attention to tasks that do not provide a high level of stimulation or reward or require sustained mental effort.
- **b** Lacking attention to detail (e.g., overlooks or misses details).
- **c** Making careless mistakes in school or work assignments (e.g., work that is inaccurate).
- **d** Difficulty following instructions and completing tasks or assignments (e.g., starts tasks but quickly loses focus and is easily side-tracked).
- **e** Difficulty sustaining attention in tasks or play activities (e.g., has difficulty remaining focused during classes, conversations, or lengthy reading).
- **f** Easily distracted by extraneous stimuli or thoughts not related to the task at hand.
- **g** Often does not seem to listen when spoken to directly (e.g., mind seems elsewhere, even in the absence of any obvious distraction, frequently appears to be daydreaming or to have mind elsewhere).
- **h** Difficulty planning, managing and organising schoolwork, tasks and other activities (e.g., difficulty managing sequential tasks; difficulty keeping materials and belongings in order; messy, disorganised work; poor time management; fails to meet deadlines).
- **i** Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., schoolwork or homework; for older adolescents and adults, preparing reports, completing forms, reviewing lengthy papers).
- **j** Often loses things necessary for tasks or activities (eg, school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, and mobile telephones).
- **k** Is often forgetful in daily activities (e.g., doing chores, running errands; for older adolescents and adults, returning calls, paying bills, keeping appointments).
- **l** Note: inattention may not be evident when engaged in activities that provide intense stimulation and frequent rewards.

II. Hyperactivity and impulsivity: Several of the following symptoms have persisted for at least six months to a degree that is inconsistent with developmental level, negatively impacting social and academic/occupational activities (these tend to be most evident in structured situations that require behavioural self-control):

- **a** May show features of excessive motor activity, particularly when required to be still.
- **b** Often fidgets with or taps hands or feet or squirms in seat
- **c** Often leaves seat in situations when remaining seated is expected (e.g., in the office or other workplace, or in other situations that require remaining in place).
- **d** Often runs about or climbs in situations where it is inappropriate. (Note: In adolescents or adults, these impulses may be limited to feeling restless, a sense of discomfort with being quiet or still).
- **e** Often unable to play or engage in leisure activities quietly.
- **f** Is often "on the go", acting as if "driven by a motor" (e.g., is unable to be, or uncomfortable being, still for extended time, as in restaurants, meetings; may be experienced by others as being restless or difficult to keep up with).
- **g** Often talks excessively.
- **h** Often blurts out an answer before a question has been completed (e.g., completes people's sentences; cannot wait for turn in conversation). In adults, may comment impulsively at work.
- **i** Often has difficulty waiting one's turn (e.g., while waiting in line).
- **j** Often interrupts or intrudes on others (e.g., butts into conversations, games, or activities; may start using other people's things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing).
- **k** Tendency to act in response to immediate stimuli without deliberation or consideration of risks and consequences (e.g., engaging in behaviours with the potential for physical injury, impulsive decisions, reckless driving).

Table 14.1. (continued)

2. Several significant inattentive or hyperactive-impulsive symptoms were present prior to age 12 years (although clinical attention and presentation may only be later).
3. Manifestations of inattentive or hyperactive-impulsive symptoms are present in multiple settings (e.g., at home, school, or work; with friends or relatives; in other activities), but might vary according to the structure and demands of the setting.
4. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.
5. The symptoms are not better accounted for by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, personality disorder), medication (e.g., bronchodilators, thyroid replacement), substance use (e.g., stimulants) or other medical conditions including disease of the nervous system.
Specify whether: • **Combined presentation:** If diagnostic requirements of ADHD are met, with presence of clinically significant symptoms of both inattention and hyperactivity- impulsivity at current presentation, with neither clearly predominating. • **Predominantly inattentive presentation:** If diagnostic requirements for ADHD are met and symptoms of inattention are predominant. • **Predominantly hyperactive/impulsive presentation:** If diagnostic requirements of ADHD are met and symptoms of hyperactivity-impulsivity are predominant.

combined pharmacotherapy and behavioural intervention appeared particularly useful for some additional measures (i.e., academic achievement, social skills).[8] Current consensus guidelines recommend a combination of psychosocial/behavioural and pharmacologic interventions, depending on age and severity of symptoms.[9,10]

We have focused the algorithm on the treatment of children and adolescents with ADHD as opposed to adults, although the approach is generally similar.

STEP 1: DIAGNOSIS OF ADHD

The diagnosis of ADHD can be made by a health professional with training and expertise in the diagnosis of ADHD.[9] The diagnosis should be based on a full clinical and psychosocial assessment and observer reports or observations in a variety of settings, as well as a mental state examination. Diagnosis can only be made when symptoms of hyperactivity/impulsivity and/or inattention meet the DSM-5 criteria or are consistent with ICD-11 guidelines and are associated with at least moderate impairment in multiple settings (see Table 14.1.). Rating scales may be used as an adjunct to help assess the child, but are not diagnostic tools.[10] Patients with hyperactive or impulsive symptoms are more likely to be referred for treatment than those with primarily inattentive symptoms, although both may benefit equally from treatment.[11] The diagnosis should not be made in very young children (under six years) without specialist input.

Target symptoms of treatment may include motor restlessness, behavioural disturbances and social difficulties. Children and adolescents with ADHD are at increased risk of mood and anxiety disorders, conduct and oppositional defiant disorder, and intellectual disabilities.[12,13]

STEP 2: COMPLICATIONS IN DIAGNOSIS IMPACTING PHARMACOTHERAPY

Up to one-half of children with ADHD have one or more comorbid behavioural or emotional disorders.[14] ADHD can be complicated in a number of ways that may affect pharmacotherapy decisions:

a. **Comorbid conduct disorder:** Standard treatments for ADHD may impact positively on comorbid conduct disorder.[13] However, patients with significant conduct disorders are likely to require particular emphasis on behavioural modification by means of family intervention and limit-setting to address symptoms, combined with patient/parent education and support.[15]
b. **Comorbid learning disorders:** Standard treatments for ADHD may again impact positively on comorbid learning disorder.[10]

However, patients with significant learning disorders are likely to require additional remedial educational interventions to address scholastic problems.

c. **Comorbid depression or anxiety:** Depressive and anxiety disorders occur more commonly in children and adolescents with ADHD than those without[16,17], and should prompt specialist consultation. The combination of pharmacological and non-pharmacological treatments may have additional benefit in this population.[18]
d. **Comorbid tics:** Although stimulants have not been shown to worsen tics in most people with tic disorders[19] and remain first-line, they may exacerbate tics in individual cases.[20,21] In these instances, treatment with α-agonists (clonidine) or atomoxetine may be an alternative.[21]
e. **Alcohol and/or substance abuse or dependence:** Children with ADHD are more likely than peers to develop substance-use disorders (SUDs), and treatment with stimulants may reduce the risk of SUD.[22-24] Despite this, stimulants themselves are a class of medication with significant abuse and diversion potential.[25] In patients with ADHD and a comorbid SUD, non-stimulants may be an appropriate alternative for patients with concern about abuse and physicians concerned with general misuse. Where prescribed, higher doses of stimulants may be required in ADHD and comorbid SUD.[24]
f. **History of psychosis:** Stimulants may precipitate and/or exacerbate psychosis in susceptible patients.[26] However, there is no evidence to suggest that psychotic symptoms occur more frequently in children treated with ADHD drugs than in those in the general population.[27] If psychotic symptoms do occur with therapeutic doses of ADHD medications, an appropriate strategy would involve reductions in the dose, or discontinuation of the ADHD medications, with a re-challenge once the psychotic symptoms have resolved.[27,28] Simultaneous use of antipsychotic medication may also be considered.[28]
g. **Pregnancy/lactation:** Limited data suggest that stimulants are safe to use in pregnancy and lactation, although there are risks associated with both continuing and discontinuing medications.[29] Both methylphenidate and atomoxetine have been associated with an increased risk of spontaneous abortion, however these findings may be influenced by confounding factors (for example, maternal smoking status).[30]
h. **Adverse psychosocial circumstances:** Medication alone may not be useful when psychosocial circumstances contribute to the exacerbation of ADHD symptoms. Family intervention (in the form of behaviour modification) and school-based contingency management may be crucial first steps if pharmacotherapy is to succeed.[31]

STEP 3: FIRST-LINE PHARMACOTHERAPY

Prior to starting pharmacotherapy, a detailed assessment should take place, including a full history and physical examination with attention to the cardiovascular system.[32] Heart rate, blood pressure, height and weight should be plotted on centile and growth charts respectively. An ECG is indicated if there is a past medical or family history of serious cardiac disease, a history of sudden death in young family members, or abnormal findings on cardiac examination.

Although the algorithm (see Figure 4.1.1.) focuses on the pharmacotherapy of ADHD, it is worth noting that behavioural and psychological treatments may be indicated as first-line treatment in children with very mild ADHD, and in those under the age of six years.[9]

First-line pharmacotherapy includes stimulant and non-stimulant medication; we recommend stimulant medication as first-line treatment in ADHD.[9]

Stimulant medication: Methylphenidate is the most widely prescribed of these agents, with a rapid onset of action and a long record of safety and efficacy.[33,34] Various short-acting, intermediate-release and long-acting forms are available, and may be prescribed according to the individual patient's needs. A reasonable starting dose is 5 mg, three times daily, or equivalent for extended-release formulations. Methylphenidate is also an effective and safe medication in the treatment of adult ADHD.[34-36]

Amphetamine-type stimulants are recommended within their licensed indications for treatment of ADHD, but are not available in South Africa.[37,38]

Non-stimulant medication: Atomoxetine is a serotonin-noradrenaline re-uptake inhibitor (SNRI) that may be used when there are contra-indications to treatment with stimulants, such as a comorbid substance-use disorder or parental risk of abuse and diversion of stimulants. Atomoxetine is safe, well-tolerated and effective in reducing the core symptoms of ADHD[39-41], and is prescribed at a dose of 0.5 mg/kg/day-1.2 mg/kg/day. Like stimulant medication, atomoxetine is also an effective treatment in adults with ADHD, although may be more useful for inattention rather than impulsivity/hyperactivity.[42,43]

STEP 4: ASSESS RESPONSE TO TREATMENT

To determine response to medication, it is important to ask about change in those symptoms initially targeted for treatment. It may be useful to have family and teachers complete a scale to rate ADHD symptoms to quantify response to medication – the Swanson, Nolan and Pelham Teacher and Parent Rating Scale (SNAP-IV) is one example; it is free to download and has good psychometric properties.[44,45]

Side effects of stimulants include loss of appetite, loss of weight, growth delay and insomnia. Cardiovascular side effects are rare, although arrhythmia may occur.[32] It is also important to monitor for the development of psychosis.[32] Height, weight, blood pressure and pulse should continue to be monitored during maintenance treatment. Side effects may respond to adjustments in dosing or timing (e.g., restricting use to mornings and early afternoons).[46] Decrease in physical stature has been raised as a concern, but the use of drug holidays during school vacations may allow for catch-up growth.[47]

When the patient has a good response to medication, it is important to reinforce the necessity for continuing the medication at the therapeutic dose despite such improvement. Drug holidays during school vacations are no longer routinely recommended, but may be useful in the management of stimulant medication-related side effects.[47]

STEP 5: OPTIMISE DOSE AND DURATION

When there is a poor response to medication, it is important to optimise dosage and duration of treatment.

Some effects of methylphenidate can usually be seen immediately after initiation if the dose is correct. In particular, there may be an increase in the ability to concentrate and a decrease in hyperactivity. Nevertheless, to see shifts in such measures as academic and social functioning, it may be necessary to continue methylphenidate for several months. It may also be necessary to increase the dose to achieve therapeutic levels.[9] The optimal dose is the dose at which target symptoms are relieved with minimal side effects. For example, a dose of 1 mg/kg/ day of methylphenidate may be necessary in some children. A maximum dose of 60 mg per day should not be exceeded.

It is also important to ensure that medication is given throughout the day (e.g., two to three times daily), or to use an extended-release preparation if available – longer-acting preparations may improve adherence and reduce stigma.[48] Failure to administer medication at school may mean good symptom reduction in the early morning, with rebound effects as the medication wears off as the day progresses. Atomoxetine has a slower onset of action than stimulants – this is important as an adequate trial is at least 12 weeks on a therapeutic dose.[49] The maximum dose is 1.2 mg/kg/day.

STEP 6: MAINTENANCE OF TREATMENT

Patients should be re-assessed at the end of a clinical trial of optimal dosage and duration. When the patient has a good response to medication, it is important to reinforce the necessity for continuing the medication at the therapeutic dose despite the improvement. There is good evidence that both stimulants and non-stimulants are efficacious treatments in the long-term treatment of ADHD.[34]

STEP 7: RE-ASSESSMENT

When ADHD does not respond to a clinical trial of optimal dose and duration, it is useful to re-assess a number of factors. The presence of certain features may impact on the choice of the subsequent intervention.

a. **Adherence:** It is likely that clinicians often overestimate the adherence of their patients.[50] Children are likely to forget to take midday medication unless there is adequate school supervision. Many families worry that medication is addictive or a 'crutch'. It is well worth checking whether

medication is, in fact, being taken on a daily basis in a regular way.

b. **Anxiety or mood disorder:** These disorders may be misdiagnosed as ADHD. Alternatively, comorbid anxiety or mood disorders may require appropriate intervention.[51]
c. **Comorbid substance use:** In patients who fail to respond to pharmacotherapy of ADHD, the possibility of comorbid substance use should be considered. There may be a need to detoxify the patient before treating the ADHD.[22]
d. **Underlying medical disorder:** ADHD patients who fail to respond to medication should be thoroughly re-assessed for an underlying medical disorder.
e. **Psychosocial issues:** Psychosocial circumstances that continue to complicate the course of ADHD need to be assessed, as these may necessitate appropriate intervention.

STEP 8: TREATMENT RESISTANCE

Most patients with ADHD will respond to systematic pharmacotherapy or a multimodal treatment programme.[31,52] Atomoxetine is a reasonable second-line option when stimulant medications have failed to achieve adequate response or proved intolerable.[9] The evidence for the use of modafinil as a treatment for ADHD in children is still limited, compared with standard treatments.[34]

Alpha-2 adrenergic agonists (e.g., clonidine), or tricyclic antidepressants usually are reserved for children or adolescents who respond poorly to a trial of stimulants or atomoxetine, have unacceptable side effects with stimulants or atomoxetine, or have significant comorbid conditions.[53,54] For patients demonstrating an incomplete response on stimulants or atomoxetine, the α2-agonists may be used as augmenting agents.[55-57] A recent review of bupropion suggested it may have comparable tolerability, acceptability and efficacy as methylphenidate, although findings are still considered preliminary.[58] Regardless, use of these medications is best done in consultation with a specialist.

Polyunsaturated fatty acids may also improve the core symptoms of ADHD, although the evidence for this is limited.[59,60] No evidence exists to support the use of meditation and acupuncture (as alternative therapies) in treating ADHD.[61,62]

ADDITIONAL READING

1. Bolea-Alamanac B, Nutt DJ, Adamou M, *et al*. Evidence-based guidelines for the pharmacological management of attention deficit hyperactivity disorder: Update on recommendations from the British Association for Psychopharmacology. J Psychopharmacol. 2014;28(3):179-203.
2. Cortese S, Adamo N, Del Giovane C, *et al*. Comparative Efficacy and Tolerability of Medications for Attention-Deficit Hyperactivity Disorder in Children, Adolescents, and Adults: A Systematic Review and Network Meta-Analysis. The Lancet Psychiatry. 2018 Sep 1;5(9):727-38.
3. Daley D, van der Oord S, Ferrin M, *et al*. Behavioral Interventions in Attention-Deficit/Hyperactivity Disorder: A Meta-Analysis of Randomized Controlled Trials Across Multiple Outcome Domains. J Am Acad Child Adolesc Psychiatry. 2014;53(8):835-47, 47 e1-5.
4. Efron D. Attention-deficit/hyperactivity disorder: The past 50 years. J Paediatr Child Health. 2015;51(1):69-73.
5. Hirota T, Schwartz S, Correll CU. Alpha-2 Agonists for Attention-Deficit/Hyperactivity Disorder in Youth: A Systematic Review and Meta-Analysis of Monotherapy and Add-On Trials to Stimulant Therapy. J Am Acad Child Adolesc Psychiatry. 2014;53(2):153-73.
6. Clemow DB, Walker DJ. The potential for misuse and abuse of medications in ADHD: A review. Postgrad Med. 2014;126(5):64-81.
7. Ibrahim K, Donyai P. Drug holidays from ADHD medication: International experience over the past four decades. J Atten Disord. 2014.
8. National Institute for Health and Care Excellence. Attention deficit hyperactivity disorder: Diagnosis and management [Internet]. [London]: NICE; 2018 [updated 2019 Sep; cited 2022 May 23]. (NICE guideline [NG87]). Available from: https://www.nice.org.uk/guidance/ng87.

REFERENCES

1. Polanczyk GV, Willcutt EG, Salum GA, *et al*. ADHD Prevalence Estimates Across Three Decades: An Updated Systematic Review and Metaregression Analysis. Int J Epidemiol. 2014;43(2):434-42.
2. Posner J, Polanczyk GV, Sonuga-Barke E. Attention-deficit hyperactivity disorder. The Lancet. 2020 Feb;395(10222):450-62.
3. Simon V, Czobor P, Bálint S, *et al*. Prevalence and Correlates of Adult Attention-Deficit Hyperactivity Disorder: Meta-Analysis. Br J Psychiatry J Ment Sci. 2009 Mar;194(3):204-11.
4. Sharma A, Couture J. A review of the pathophysiology, etiology, and treatment of attention-deficit hyperactivity disorder (ADHD). Ann Pharmacother. 2014;48(2):209-25.

5. Efron D. Attention-deficit/hyperactivity disorder: The past 50 years. J Paediatr Child Health. 2015;51(1):69-73.
6. Clemow DB, Walker DJ. The potential for misuse and abuse of medications in ADHD: A review. Postgrad Med. 2014;126(5):64-81.
7. Shaw M, Hodgkins P, Caci H, *et al*. A Systematic Review and Analysis of Long-Term Outcomes in Attention Deficit Hyperactivity Disorder: Effects of Treatment and Non-Treatment. BMC Med. 2012;10:99.
8. The MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. Multimodal Treatment Study of Children with ADHD. Arch Gen Psychiatry. 1999;56(12):1073-86.
9. National Institute for Health and Care Excellence. Attention deficit hyperactivity disorder: Diagnosis and management [Internet]. [London]: NICE; 2018 [updated 2019 Sep; cited 2022 May 23]. (NICE guideline [NG87]). Available from: https://www.nice.org.uk/guidance/ng87.
10. Bolea-Alamanac B, Nutt DJ, Adamou M, *et al*. Evidence-based guidelines for the pharmacological management of attention deficit hyperactivity disorder: Update on recommendations from the British Association for Psychopharmacology. J Psychopharmacol. 2014;28(3):179-203.
11. Willcutt EG. The prevalence of DSM-IV attention-deficit/hyperactivity disorder: A meta-analytic review. Neurotherapeutics. 2012;9(3):490-9.
12. Tistarelli N, Fagnani C, Troianiello M, *et al*. The nature and nurture of ADHD and its comorbidities: A narrative review on twin studies. Neurosci Biobehav Rev. 2020 Feb;109:63-77.
13. Pringsheim T, Hirsch L, Gardner D, *et al*. The Pharmacological Management of Oppositional Behaviour, Conduct Problems, and Aggression in Children and Adolescents with Attention-Deficit Hyperactivity Disorder, Oppositional Defiant Disorder, and Conduct Disorder: A Systematic Review and Meta-Analysis. Part 1: Psychostimulants, Alpha-2 Agonists, and Atomoxetine. Can J Psychiatry. 2015 Feb;60(2):42-51.
14. Jensen PS, Hinshaw SP, Kraemer HC, *et al*. ADHD comorbidity findings from the MTA study: Comparing comorbid subgroups. J Am Acad Child Adolesc Psychiatry. 2001;40(2):147-58.
15. Turgay A. Treatment of comorbidity in conduct disorder with attention-deficit hyperactivity disorder (ADHD). Essent Psychopharmacol. 2005;6(5):277-90.
16. Daviss WB. A review of co-morbid depression in pediatric ADHD: Etiology, phenomenology, and treatment. J Child Adolesc Psychopharmacol. 2008;18(6):565-71.
17. Stern A, Agnew-Blais JC, Danese A, *et al*. Associations between ADHD and emotional problems from childhood to young adulthood: A longitudinal genetically sensitive study. J Child Psychol Psychiatry. 2020 Nov;61(11):1234-42.
18. Murray DW, Arnold LE, Swanson J, *et al*. A clinical review of outcomes of the multimodal treatment study of children with attention-deficit/hyperactivity disorder (MTA). Curr. Psychiatry Rep. 2008;10(5):424-31.
19. Cohen SC, Mulqueen JM, Ferracioli-Oda E, *et al*. Meta-Analysis: Risk of Tics Associated with Psychostimulant Use in Randomized, Placebo-Controlled Trials. J Am Acad Child Adolesc Psychiatry. 2015 Sep;54(9):728-36.
20. Madruga-Garrido M, Mir P. Tics and Other Stereotyped Movements as Side Effects of Pharmacological Treatment. In: International Review of Neurobiology. Elsevier; 2013. p. 481-94.
21. Osland ST, Steeves TD, Pringsheim T. Pharmacological treatment for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders. Cochrane Database Syst Rev. 2018(6):CD007990.
22. Harstad E, Levy S, Committee on Substance Abuse. Attention-deficit/hyperactivity disorder and substance abuse. Pediatrics. 2014;134(1): 293-301.
23. Srichawla BS, Telles CC, Schweitzer M, *et al*. Attention Deficit Hyperactivity Disorder and Substance Use Disorder: A Narrative Review. Cureus. 2022 Apr;14(4):e24068.
24. Özgen H, Spijkerman R, Noack M, *et al*. Treatment of Adolescents with Concurrent Substance Use Disorder and Attention-Deficit/Hyperactivity Disorder: A Systematic Review. J Clin Med. 2021 Aug 30;10(17):3908.
25. Francis AR, Weyandt LL, Anastopoulos AD, *et al*. Outcomes and Predictors of Stimulant Misuse in College Students with and without ADHD. J Atten Disord. 2022 Mar;26(5):779-93.
26. Kraemer M, Uekermann J, Wiltfang J, *et al*. Methylphenidate-induced psychosis in adult attention-deficit/hyperactivity disorder: Report of 3 new cases and review of the literature. Clin Neuropharmacol. 2010;33(4):204-6.
27. Cortese S, Holtmann M, Banaschewski T, Buitelaar J, Coghill D, Danckaerts M, *et al*. Practitioner Review: Current best practice in the management of adverse events during treatment with ADHD medications in children and adolescents. J Child Psychol Psychiatry. 2013 Mar;54(3):227-46.
28. Hechtman L. ADHD medication treatment and risk of psychosis. Lancet Psychiatry. 2019 Aug 1;6(8):632-3.
29. Bolea-Alamanac BM, Green A, Verma G, *et al*. Methylphenidate Use in Pregnancy and

Lactation: A Systematic Review of Evidence: Methylphenidate in Pregnancy and Lactation. Br J Clin Pharmacol. 2014 Jan;77(1):96-101.
30. Bro SP, Kjaersgaard MI, Parner ET, *et al*. Adverse pregnancy outcomes after exposure to methylphenidate or atomoxetine during pregnancy. Clin Epidemiol. 2015;7:139-47.
31. Fabiano GA, Schatz NK, Aloe AM, *et al*. A Systematic Review of Meta-Analyses of Psychosocial Treatment for Attention-Deficit/Hyperactivity Disorder. Clin Child Fam Psychol Rev. 2015;18(1):77-97.
32. Storebø OJ, Pedersen N, Ramstad E, *et al*. Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents – assessment of adverse events in non-randomised studies. Cochrane Database Syst Rev. 2018(5):CD012069.
33. Epstein T, Patsopoulos NA, Weiser M. Immediate-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults. Cochrane Database Syst Rev. 2014(9):CD005041.
34. Cortese S, Adamo N, Del Giovane C, *et al*. Comparative Efficacy and Tolerability of Medications for Attention-Deficit Hyperactivity Disorder in Children, Adolescents, and Adults: A Systematic Review and Network Meta-Analysis. Lancet Psychiatry. 2018 Sep;5(9):727-38.
35. Weyandt LL, Oster DR, Marraccini ME, *et al*. Pharmacological interventions for adolescents and adults with ADHD: Stimulant and nonstimulant medications and misuse of prescription stimulants. Psychol Res Behav Manag. 2014;7:223-49.
36. Boesen K, Paludan-Müller AS, Gøtzsche PC, *et al*. Extended-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults. Cochrane Database Syst Rev. 2022(2):CD012857.
37. Frampton JE. Lisdexamfetamine dimesylate: A review in paediatric ADHD. Drugs. 2018 Jul;78(10):1025-36.
38. Heal DJ, Smith SL, Gosden J, *et al*. Amphetamine, past and present – a pharmacological and clinical perspective. J Psychopharmacol Oxf Engl. 2013 Jun;27(6):479-96.
39. Liu Q, Zhang H, Fang Q *et al*. Comparative Efficacy and Safety of Methylphenidate and Atomoxetine for Attention-Deficit Hyperactivity Disorder in Children and Adolescents: Meta-Analysis Based on Head-to-Head Trials. J Clin Exp Neuropsychol. 2017 Oct 21;39(9):854-65.
40. Bushe CJ, Savill NC. Systematic review of atomoxetine data in childhood and adolescent attention-deficit hyperactivity disorder 2009-2011: Focus on clinical efficacy and safety. J Psychopharmacol. 2014;28(3):204-11.
41. Gayleard JL, Mychailyszyn MP. Atomoxetine Treatment for Children and Adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD): A Comprehensive Meta-Analysis of Outcomes on Parent-Rated Core Symptomatology. Atten Deficit Hyperact Disord. 2017 Sep;9(3):149-60.
42. Meszaros A, Czobor P, Balint S, *et al*. Pharmacotherapy of Adult Attention Deficit Hyperactivity Disorder (ADHD): A Meta-Analysis. Int J Neuropsychopharmacol. 2009;12(8):1137-47.
43. Ravishankar V, Chowdappa SV, Benegal V, *et al*. The efficacy of Atomoxetine in Treating Adult Attention Deficit Hyperactivity Disorder (ADHD): A Meta-Analysis of Controlled Trials. Asian J Psychiatry. 2016 Dec;24:53-8.
44. Hall CL, Guo B, Valentine AZ, *et al*. The validity of the SNAP-IV in children displaying ADHD symptoms. Assessment. 2020 Sep;27(6):1258-71.
45. Swanson JM. SNAP-IV 26-Item Teacher and Parent Rating Scale [Internet]. [Accessed 2022 Jun 29]. Available at: http://www.shared-care.ca/files/Scoring_for_SNAP_IV_Guide_26-item.pdf.
46. Greenhill LL, Pliszka S, Dulcan MK. Practice parameter for the use of stimulant medications in the treatment of children, adolescents, and adults. J Am Acad Child Adolesc Psychiatry. 2002 Feb;41(2):26S-49S.
47. Ibrahim K, Donyai P. Drug holidays from ADHD medication: International experience over the past four decades. J Atten Disord. 2015 Jul;19(7):551-68.
48. Coghill D, Banaschewski T, Zuddas A, *et al*. Long-Acting Methylphenidate Formulations in the Treatment of Attention-Deficit/Hyperactivity Disorder: A Systematic Review of Head-to-Head Studies. BMC Psychiatry. 2013 Dec;13(1):237.
49. Dickson RA, Maki E, Gibbins C, *et al*. Time courses of improvement and symptom remission in children treated with atomoxetine for attention-deficit/hyperactivity disorder: Analysis of Canadian open-label studies. Child Adolesc Psychiatry Ment Health. 2011 May 11;5(1):14.
50. Gajria K, Lu M, Sikirica V, *et al*. Adherence, persistence, and medication discontinuation in patients with attention-deficit/hyperactivity disorder – a systematic literature review. Neuropsychiatr Treat. 2014;10:1543-69.
51. Koyuncu A, Ayan T, Ince Guliyev E, *et al*. ADHD and Anxiety Disorder Comorbidity in Children and Adults: Diagnostic and Therapeutic Challenges. Curr Psychiatry Rep. 2022 Feb;24(2):129-40.
52. Van der Oord S, PJM Prins, Oosterlaan J, *et al*. Efficacy of Methylphenidate, Psychosocial Treatments and Their Combination in School-Aged Children with ADHD: A Meta-Analysis. Clin Psychol Rev. 2008;28(5):783-800.
53. Hirota T, Schwartz S, Correll CU. Alpha-2 Agonists for Attention-Deficit/Hyperactivity Disorder in Youth: A Systematic Review and Meta-Analysis of Monotherapy and Add-On Trials to Stimulant

Therapy. J Am Acad Child Adolesc Psychiatry. 2014;53(2):153–73.
54. Otasowie J, Castells X, Ehimare UP, *et al*. Tricyclic antidepressants for attention deficit hyperactivity disorder (ADHD) in children and adolescents. Cochrane Database Syst Rev. 2014(9):CD006997.
55. Ruggiero S, Clavenna A, Reale L, *et al*. Guanfacine for Attention Deficit and Hyperactivity Disorder in Pediatrics: A Systematic Review and Meta-Analysis. Eur Neuropsychopharmacol. 2014;24(10):157890.
56. Cutler AJ, Brams M, Bukstein O, *et al*. Response/remission with guanfacine extended-release and psychostimulants in children and adolescents with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2014;53(10):1092-101.
57. Childress AC, Sallee FR. Revisiting clonidine: An innovative add-on option for attention-deficit/hyperactivity disorder. Drugs Today. 2012;48(3):207.
58. Maneeton N, Maneeton B, Intaprasert S, *et al*. A systematic review of randomized controlled trials of bupropion versus methylphenidate in the treatment of attention-deficit/hyperactivity disorder. Neuropsychiatr Treat. 2014;10:1439-49.
59. Puri BK, Martins JG. Which polyunsaturated fatty acids are active in children with attention-deficit hyperactivity disorder receiving PUFA supplementation? A fatty acid validated meta-regression analysis of randomized controlled trials. Prostaglandins Leukot Essent Fatty Acids. Vol. 90. 2014. p. 179-89.
60. Gillies D, Sinn J, Lad SS, *et al*. Polyunsaturated fatty acids (PUFA) for attention deficit hyperactivity disorder (ADHD) in children and adolescents. Cochrane Database Syst Rev. 2012(7):CD007986.
61. Li S, Yu B, Zhou D, *et al*. Acupuncture for attention deficit hyperactivity disorder (ADHD) in children and adolescents. Cochrane Database Syst Rev. 2011(4):CD007839.
62. Krisanaprakornkit T, Ngamjarus C, Witoonchart C, *et al*. Meditation therapies for attention-deficit/hyperactivity disorder (ADHD). Cochrane Database Syst Rev. 2010(6):CD006507.

15: Drug Interactions

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This chapter describes harmful interactions that are of particular relevance to clinical practice. Drug interactions may be pharmacokinetic or pharmacodynamic in nature. Pharmacokinetic drug interactions involve interactive effects on absorption, distribution, protein-binding, metabolism and excretion; pharmacodynamic interactions occur directly at the site of action of the different drugs.[1]

Risks of drug interactions obviously increase with polypharmacy.[2] Additional factors, such as advanced age, general medical conditions, and genetic deficiencies in liver-metabolising enzymes, may also be important (for example, genetically low CYP2D6 activity may result in toxicity when two or more drugs taken concurrently are metabolised by this enzyme).[1]

This chapter discusses important harmful pharmacokinetic and pharmacodynamic interactions noted with the major psychiatric medications. A table (see Table 15.1.) of common pharmacokinetic drug interactions is included in this chapter – although this list is by no means exhaustive. We wish to emphasise that this chapter is not meant to include all known drug interactions; readers are encouraged to consult the product information sheet of all medications that they prescribe.

1. PHARMACOKINETIC DRUG INTERACTIONS

a. Absorption

The absorption of any drug from the gastro-intestinal tract is dependent on local factors, including gastric pH, motility, and surface area. For example, antacids and cimetidine reduce the absorption of many antipsychotics. Similarly, anticholinergics reduce motility and suppress gastric acid secretion, and therefore reduce absorption of other agents.

b. Protein-binding

After absorption, drugs distribute freely in blood cells or plasma, or bind to plasma proteins (albumin and glycoproteins). Drugs vary in degree of protein-binding. Competition for, and displacement from, binding sites occurs, resulting in altered ratios of bound-to-free drug. For example, many antidepressants and benzodiazepines are protein-bound, and can displace warfarin (highly protein-bound). Such effects may not manifest clinically, perhaps because the displaced drug is often rapidly metabolised.

c. Metabolism

Metabolism produces active and inactive metabolites. Two processes are important, namely enzyme induction and enzyme inhibition. Enzyme induction occurs when a drug increases the activity of a particular enzyme. Thus, carbamazepine and cigarette smoking induce a range of P450 enzymes, so reducing the availability of a range of agents taken concomitantly. Enzyme inhibition occurs when a drug reduces the activity of an enzyme. Valproate and cimetidine inhibit various P450 systems, thereby increasing blood levels of various other agents.

The hepatic cytochrome P450 enzyme system is a group of iso-enzymes involved in the oxidative metabolism of many psychiatric medications and deserves particular emphasis. There are four families of the P450 system, designated 1,2,3, and 4 (hence the nomenclature CYP3A4, where CYP represents cytochrome P450, 3 represents the family, A the enzyme subfamily, and 4 the individual gene). Important P450 enzymes in the prescription of psychiatric medications include 1A2, 2D6, and 3A4. Psychotropic medication interacts with cytochrome P450 enzymes in the liver and brain through a variety of mechanisms.[3] Individual variations in these enzymes may result in clinically important drug-drug interactions. Pharmacogenetic studies might further identify an individual's ability to absorb, distribute, metabolise or excrete various

Continued on page 160

Table 15.1. Selected CYP450 pharmacokinetic interactions

Substrate	Inhibitors	Inducers
CYP1A2		
Caffeine Chlorpromazine Clomipramine Clozapine Duloxetine Mirtazapine Melatonin Olanzapine	Fluvoxamine Ciprofloxacin Ketoconazole	Carbamazepine Cigarette smoke Barbiturates Phenobarbital
CYP2C9/19		
Diazepam Tricyclics Oral hypoglycaemics Warfarin	Fluoxetine Fluovoxamine Carbamazepine Modafinil Oxcarbazepine Valproate Fluconazole	*Ginkgo biloba*
CYP2D6		
Amphetamines Atomoxetine Aripiprazole Clomipramine Chlorpromazine Fluoxetine Galantamine Haloperidol Imipramine Mianserin Nortriptyline Olanzapine Perphenazine Risperidone Trimipramine Venlafaxine Zuclopenthixol	Amitriptyline Bupropion Duloxetine Fluoxetine Fluvoxamine Paroxetine Quinidine	None
CYP3A4		
Alprazolam Aripiprazole Buspirone Calcium-channel blockers Carbamazepine Chlorpromazine Clonazepam Clozapine Diazepam Galantamine Haloperidol Midazolam Nitrazepam Oral contraceptives Pimozide Zolpidem Zopiclone	Nefazodone Grapefruit juice Protease inhibitors Ketoconazole Clarithromycin	Phenytoin Carbamazepine Oxcarbazepine Phenobarbital *Ginkgo biloba* St. John's Wort

medications.[4,5] Indeed, a number of guidelines are now available to aid clinicians integrating pharmacogenetic data into daily clinical practice, although such testing should in most instances be restricted to specialists.[6]

d. Excretion

Significant drug interactions may result from the effects drugs have on kidney excretion. Lithium provides a few classic examples:

i. **Lithium-indomethacin combination:** Indomethacin reduces the renal blood flow (by reducing prostaglandin synthesis) and so increases serum lithium levels. This may also occur with other nonsteroidal anti-inflammatory drugs, such as ibuprofen.
ii. **Lithium-thiazide combination:** Thiazide increases lithium levels.
iii. **Lithium-salt:** By affecting renal sodium excretion, salt restriction increases serum lithium levels, while salt intake reduces serum-lithium levels.

2. PHARMACODYNAMIC DRUG INTERACTIONS

These are interactions that occur at the site of action of the drugs in question. Clinically relevant examples include:

- Potentially fatal 'serotonin syndrome' that can result when MAOIs are administered concomitantly with SSRIs.
- Potentiation of CNS-depressant effects when alcohol, benzodiazepines, tricyclic antidepressants, or antipsychotics are taken concomitantly.
- Enhancement of anticholinergic effects when drugs with high anticholinergic activity (e.g., tricyclic antidepressants or certain antipsychotics) are administered together with anticholinergics.

3. SPECIFIC PSYCHOTROPIC DRUG INTERACTIONS

a. Antidepressants

Most antidepressants are metabolised by, or inhibit to a varying degree, one or more P450 enzymes. CYP2D6, for example, metabolises a number of antidepressants (including TCAs, SSRIs [fluoxetine, paroxetine, fluoxetine], and venlafaxine) and is inhibited by fluoxetine and paroxetine. CYP3A4 metabolises sertraline, is activated by St John's Wort, and is inhibited by fluvoxamine. There may be marked genetic variation in the activity of these enzymes. Combinations of MAOIs and other antidepressants are contra-indicated, given the potential to cause serotonin syndrome.

b. Antipsychotics

Antipsychotics often inhibit the CYP2D6 enzyme and may reduce the ability of the liver to metabolise some drugs. Conversely, other drugs that inhibit CYP2D6 may raise the levels of antipsychotics. Low-potency typical antipsychotics have the propensity to potentiate the anticholinergic, sedative and hypotensive effects of the tricyclic antidepressants. Pimozide should not be taken concomitantly with foods (e.g., grapefruit juice) or medications (e.g., clarithromycin, erythromycin, fluvoxamine, ketoconazole) that inhibit the CYP3A4 enzyme, as this may lead to increased drug levels and prolongation of the QTc-interval. Clozapine should not be used with drugs that cause bone-marrow suppression (e.g., carbamazepine, captopril, propylthiouracil, sulphonamides) given the possibility of agranulocytosis.

c. Benzodiazepines

Many of the benzodiazepines and non-benzodiazepine hypnotics are metabolised by CYP3A4. Antiretrovirals (specifically protease inhibitors) may increase the serum levels of benzodiazepines due to their inhibition of CYP3A4. Benzodiazepines may, as noted previously, enhance the sedative effects of alcohol, antidepressants, and antipsychotics.

ADDITIONAL READING

1. Sandson NB, Armstrong SC, Cozza KL. An overview of psychotropic drug-drug interactions. Psychosomatics. 2005;46(5):464-94.
2. Spina E, Santoro V, D'Arrigo C. Clinically relevant pharmacokinetic drug interactions with second-generation antidepressants: An update. Clin Ther. 2008;30(7):1206-27.
3. Kennedy WK, Jann MW, Kutscher EC. Clinically significant drug interactions with atypical antipsychotics. CNS Drugs. 2013;27(12):1021-48.
4. Taylor DM, Barnes TR, Young AH. The Maudsley Prescribing Guidelines in Psychiatry. 14th edition. Chichester, West Sussex. Hoboken, NJ: John Wiley & Sons; 2021.

REFERENCES

1. Taylor DM, Barnes TR, Young AH. The Maudsley Prescribing Guidelines in Psychiatry. 14th edition. Chichester, West Sussex. Hoboken, NJ; John Wiley & Sons; 2021.

2. Kukreja S, Kalra G, Shah N, *et al.* Polypharmacy in psychiatry: A review. Mens Sana Monogr. 2013;11(1):82-99.
3. Daniel WA, Bromek E, Danek PJ, *et al.* The mechanisms of interactions of psychotropic drugs with liver and brain cytochrome P450 and their significance for drug effect and drug-drug interactions. Biochem Pharmacol. 2022 May 1;199:115006.
4. Van Westrhenen R, van Schaik RHN, van Gelder T, *et al.* Policy and practice review: A first guideline on the use of pharmacogenetics in clinical psychiatric practice. Front Pharmacol. 2021;12.
5. Fabbri C, Porcelli S, Serretti A. From pharmacogenetics to pharmacogenomics: The way toward the personalization of antidepressant treatment. Can J Psychiatry. 2014;59(2):62-75.
6. Abdullah-Koolmees H, van Keulen AM, Nijenhuis M, *et al.* Pharmacogenetics guidelines: Overview and comparison of the DPWG, CPIC, CPNDS, and RNPGx guidelines. Front Pharmacol. 2021;11.

Notes