The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders: Major depression summary

AUTHOR(S)

G S Malhi, E Bell, Ajeet Singh, D Bassett, Michael Berk, P Boyce, R Bryant, M Gitlin, A Hamilton, P Hazell, M Hopwood, B Lyndon, R S McIntyre, G Morris, R Mulder, R Porter, L N Yatham, A Young, G Murray

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The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders: Major depression summary

Gin S. Malhi[1,2,3] | Erica Bell[1,2,3] | Ajeet B. Singh[4] | Darryl Bassett[5] | Michael Berk[6,7] | Philip Boyce[8,9] | Richard Bryant[10] | Michael Gitlin[11] | Amber Hamilton[1,2,3] | Philip Hazell[9] | Malcolm Hopwood[12] | Bill Lyndon[1] | Roger S. McIntyre[13] | Grace Morris[1,2,3] | Roger Mulder[14] | Richard Porter[14] | Lakshmi N. Yatham[15] | Allan Young[16,17] | Greg Murray[18]

[1]Department of Psychiatry, Northern Clinical School, Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia

[2]Academic Department of Psychiatry, Royal North Shore Hospital, Northern Sydney Local Health District, St Leonards, NSW, Australia

[3]CADE Clinic, Royal North Shore Hospital, Northern Sydney Local Health District, St Leonards, NSW, Australia

[4]The Geelong Clinic Healthscope, IMPACT – Institute for Mental and Physical Health and Clinical Translation, School of Medicine, Deakin University, Geelong, VIC, Australia

[5]Consultant Psychiatrist, Perth, WA, Australia

[6]IMPACT – the Institute for Mental and Physical Health and Clinical Translation, School of Medicine, Barwon Health, Deakin University, Geelong, Australia

[7]Orygen, The National Centre of Excellence in Youth Mental Health, The Florey Institute and the Department of Psychiatry, The University of Melbourne, Parkville, Vic., Australia

[8]Department of Psychiatry, Westmead Hospital and the Westmead Clinical School, Wentworthville, NSW, Australia

[9]Discipline of Psychiatry, Sydney Medical School, Faculty of Medicine and Health, University of Sydney, Sydney, NSW, Australia

[10]School of Psychology, University of New South Wales, Sydney, NSW, Australia

[11]Department of Psychiatry, Geffen School of Medicine at UCLA, Los Angeles, CA, USA

[12]Department of Psychiatry, University of Melbourne and Professorial Psychiatry Unit, Albert Road Clinic, Melbourne, Vic., Australia

[13]Mood Disorders Psychopharmacology Unit, University Health Network, Toronto, ON, Canada

[14]Department of Psychological Medicine, University of Otago, Christchurch, New Zealand

[15]Department of Psychiatry, University of British Columbia, Vancouver, British Columbia, Canada

[16]Department of Psychological Medicine, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London, UK

[17]South London and Maudsley NHS Foundation Trust, Bethlem Royal Hospital, Beckenham, UK

[18]Centre for Mental Health, Swinburne University of Technology, Hawthorn, VIC, Australia

Correspondence
Gin S Malhi, Department of Psychiatry, Northern Clinical School, Faculty of Medicine and Health, The University of Sydney, Sydney, New South Wales, Australia.
Email: gin.malhi@sydney.edu.au

Abstract

Objectives: To provide a succinct, clinically useful summary of the management of major depression, based on the 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders (MDcpg[2020]).

Methods: To develop the MDcpg[2020], the mood disorders committee conducted an extensive review of the available literature to develop evidence-based recommendations (EBR) based on National Health and Medical Research Council (NHMRC) guidelines. In the MDcpg[2020], these recommendations sit alongside consensus-based

recommendations (CBR) that were derived from extensive deliberations of the mood disorders committee, drawing on their expertise and clinical experience. This guideline summary is an abridged version that focuses on major depression. In collaboration with international experts in the field, it synthesises the key recommendations made in relation to the diagnosis and management of major depression.

Results: The depression summary provides a systematic approach to diagnosis, and a logical clinical framework for management. The latter begins with *Actions*, which include important strategies that should be implemented from the outset. These include lifestyle changes, psychoeducation and psychological interventions. The summary advocates the use of antidepressants in the management of depression as *Choices* and nominates seven medications that can be trialled as clinically indicated before moving to *Alternatives* for managing depression. Subsequent strategies regarding Medication include Increasing Dose, Augmenting and Switching (MIDAS). The summary also recommends the use of electroconvulsive therapy (ECT), and discusses how to approach non-response.

Conclusions: The major depression summary provides up to date guidance regarding the management of major depressive disorder, as set out in the MDcpg[2020]. The recommendations are informed by research evidence in conjunction with clinical expertise and experience. The summary is intended for use by psychiatrists, psychologists and primary care physicians, but will be of interest to all clinicians and carers involved in the management of patients with depressive disorders.

KEYWORDS
depression, guideline, mood disorders, treatment

1 | INTRODUCTION

The Royal Australian and New Zealand College of Psychiatrists has published clinical practice guidelines for mood disorders (MDcpg[2020])[1] updating earlier guidelines published in 2015 (MDcpg[2015]).[2] The objective of this paper is to provide a summary of these guidelines as they pertain to the management of depression. They are intended principally for psychiatrists, psychologists and primary care physicians, but will also be useful to nursing and allied mental health staff. They may also be of interest to patients and health service administrators.

The present summary document aims to serve as a ready reference for clinicians. Readers wanting more comprehensive information are encouraged to consult the more detailed and contextualised MDcpg[2020], and other contemporary guidelines for the management of depression.

The composition of the mood disorders committee, and the methods used to develop the full guidelines, are detailed in the MDcpg[2020]. For the purposes of this summary, additional members with mood disorders expertise and extensive experience of international guideline development were co-opted to ensure the recommendations within the summary have relevance worldwide.

Adhering to the principles of the MDcpg[2020], the present summary makes two types of recommendations that reflect the deliberations used to formulate advice. First, evidence-based recommendations (EBRs) were formulated using the Australian National Health and Medical Research Council (NHMRC) levels of evidence for treatment studies[3] and graded accordingly (e.g. EBR level I, II, etc). Second, where the existing evidence base for an intervention was insufficient, absent or its clinical impact and relevance uncertain, the committee members used their expertise and clinical experience to develop a consensus on its clinical usefulness, and this formed a consensus-based recommendation (CBR). It is important to note that the process involved extensive discussion and iteration of information, and that it was subject to revision in light of new information and feedback from expert consultation and peer review.

2 | EPIDEMIOLOGY

Globally, the 12-month prevalence of clinical depression, also known as major depression or major depressive disorder (MDD)

is 6%, and the risk of MDD over a lifetime is approximately double this (11.1%–14.6%).[4] Therefore, MDD is a common disorder that is found in all countries in the world, irrespective of GDP, and one in five people will suffer from an episode of depression in their lifetime. Aetiologically, while societal and environmental factors play a significant role in the psychosocial development of depression, underlying biological and genetic factors also remain key drivers, and the two interact via epigenetic mechanisms.[5] In practice, depression presents most commonly in primary care settings, first emerging from mid-adolescence, right through to the fourth and fifth decade of life. For many, the illness begins in their twenties, but a significant number will experience their first episode of depression in the second decade of life—before they turn 20.[6-9]

Major depressive disorder is twice as common in women as men, a gender difference that sets it apart from bipolar disorder.[7,10] Its onset is often insidious but at times can be sudden when, for example, it is triggered by significant life events. In most cases, the precise nature and trajectory of the illness is unpredictable and highly variable, although the course is, by and large, episodic and, generally speaking, patients tend to feel their 'normal' selves in between episodes of severe illness. However, the underlying vulnerability for depression remains even when patients are well.

By their very nature, the symptoms of depression wax and wane, and when evident, aggregate as syndromes that form the basis for depressive disorders. The diagnosis of depression is therefore regarded categorically even though the symptoms of the illness are clearly dimensional. Therefore, in practice, the diagnosis of depression is also partly contingent on the degree of distress and functional impairment the patient experiences. Depressive disorders can be further specified according to severity and syndromal subtypes—both of which may impact optimal management. In this context, the Activity, Cognition and Emotion (ACE) model[11] emphasises both the dimensional nature of depressive symptoms and the need for a longitudinal perspective and ensures a more granular appreciation of depression. Approaches such as these are particularly important when characterising depression in clinical practice as there are no accurate diagnostic biomarkers that supplant clinical acumen.

Untreated, episodes of depression typically last several months and sometimes years, and even with treatment, full recovery can take up to a year.[12] Furthermore, after recovery, the likelihood of recurrence remains high, with up to 50% of patients experiencing further episodes of depression in their lifetime. Notably, the likelihood of a favourable outcome diminishes with older age of onset, and the probability of further recurrences increases with each episode. Overall, approximately 50% of those affected by a major depressive episode recover within 6 months, and this increases to nearly 75% within a year.[13,14] However, over a quarter remain unwell and develop a chronic depressive disorder, explaining in part the high global burden of disease exerted by depression, and why it is predicted that by 2030 the illness will be the leading cause of burden of disease worldwide.[15]

3 | AETIOLOGY AND PATHOGENESIS OF DEPRESSION

It is recognised that the factors that lead to the development of depression are multiple, complex, variable and span both biopsychosocial and lifestyle domains.[16] Therefore, the processes that ultimately lead to the emergence of depressive syndromes are sophisticated and result in a range of clinical manifestations. Changes in a number of domains are known to contribute to the development and course of depression, and key amongst these are genetics,[17] stress,[18] the environment (with epigenetically mediated gene-environment interactions[19]), coping strategies and circadian function.[20] Therefore, while broad patterns exist, it is important to remember that pathogenic pathways and ultimate presentations of depression will be unique to each patient.

4 | DIAGNOSIS

The major international classificatory systems used to diagnose depression are the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5),[21] and the International Classification of Diseases, 11th revision (ICD-11).[22] Although there are subtle differences, in both nosologies, a depressive syndrome is defined on the basis of specific sets of symptoms being present which reach a clinical threshold when distress and/or dysfunction stemming from these symptoms becomes problematic for the sufferer. Ideally, a diagnosis of depression should be made after adopting a number of perspectives – gauging severity for example as mild, moderate or severe and subtyping symptoms where possible into recognisable patterns such as melancholia. In addition, the symptoms can be grouped according to the ACE model,[11] which then provides additional specificity as regards which domains need to be targeted by treatments. By employing all of these approaches concurrently, a diagnosis of depression can be achieved with reasonable precision.[23]

5 | CLASSIFICATION

As stated in the objectives, the present summary focuses primarily on major depression because this is the most common expression of depressive disorders. Note, only DSM-5 criteria are illustrated in Figure 1, and these have been positioned on the subjective-objective continuum, depending on how they can be elicited. The limitations of this symptom checklist approach mean that in practice it is advisable (as mentioned above) to additionally consider diagnosis on the basis of *severity* and specific symptom patterns that may conform to *subtypes* and *dimensions* within *ACE*[11,24] (for further discussion, see the 2020 Guideline[1] and Malhi and Bell, 2019[25]).

Clinically, over the course of the illness, the symptoms used to define episodes of depression are often absent, or if they are evident, then they are subsyndromal. This means that it is the acute

episodes of illness that hold diagnostic significance. Therefore, in addition to examining symptoms cross-sectionally, it is important to maintain a longitudinal perspective. Typically, over the course of the illness, major depression is characterised by recurrent depressive episodes that consist of acute exacerbations associated with distress and functional impairment. The characteristics of these episodes are often consistent over time, though it is important to note that individuals can experience different subtypes of depression at different times in their lives, or even manifest two 'types' of depression concurrently[a].

6 | MANAGEMENT OF DEPRESSION

6.1 | Principles and paradigms

6.1.1 | Response, remission, recovery, resilience

The aim of acute treatment is to reduce symptoms and achieve full remission and functional recovery from a depressive episode. Note, this does not cure the illness, and once the symptoms of depression manifest, indicating that the person has a depressive disorder, the person retains a vulnerability for future episodes. However, many individuals will only suffer a single episode in their lifetime.

In clinical trials, the overall impact of a depressive episode is gauged by its severity, which is usually quantified by summing the scores of individual symptoms. This crude score provides a rough measure of the overall severity of the illness, but it is not particularly informative regarding the clinical profile of the illness or its functional impairment, or indeed the 'lived experience' of the patient. This is partly why rating scales are not widely used in clinical practice. However, the use of a suitable rating scale to track the severity of clinical depression longitudinally, and in particular, to assess changes with respect to treatment, can be helpful and therefore their use is encouraged in the context of ongoing management.

In practice, *response* is equated to improvement, and terms such as remission and recovery are often used interchangeably, even though they have distinct meanings. In clinical trials, response and remission are used to evaluate the efficacy of treatments. A *response* is generally defined as at least a 50% reduction in overall symptom severity, and when the total symptom score on a rating scale falls below a pre-specified threshold on a particular scale (e.g. score of ≤10 on MADRS or ≤7 on HAM-D), the individual is said to be in *remission*. It is important to note that at this point the person is still receiving treatment, and technically only once this has stopped (and the person remains well) can they be regarded as having achieved *recovery*[b]. However, clinically, patients who maintain treatment and are well can be regarded as having recovered. Thus, for practical purposes, recovery is defined as the patient experiencing sustained clinical and functional remission for a substantial period of time.

Over recent years, the focus of management has moved from response, through remission to recovery, and now the focus is shifting further to building resilience so as to prevent relapse and future recurrence.

Resilience in the management of depression has been formulated as an adaptive process that can defend against depression through strengthening processes such as tempering and fortification.[26] This presents an opportunity for building resilience, initially through psychological interventions. The impact of acute depressive episodes on aspects of brain function appears to be cumulative, and therefore the severity and duration of these periods of illness should be limited as much as possible, and future recurrences prevented. To achieve this, prompt detection and accurate diagnosis are key, and the identification of specific early warning signs in an individual known to have depression is a vital part of ongoing management. As stress is a key driver for relapse, developing better stress management skills is a cornerstone of resilience building and helps reduce the risk of future relapses.

6.1.2 | Diagnostic and management formulation of depression

Taking a complete and thorough history, ideally over a period of time, which allows the observation of symptoms, and the gathering of collateral history, is the key to making a valid diagnosis and fully understanding depression. But to make sense of the illness as a whole, a comprehensive picture of the person's life is needed. Therefore, after assessing the current symptoms (*presenting complaint*) and how these have emerged (*history of presenting complaint*), and then reviewing previous episodes and the course of the illness as a whole (*past psychiatric history*), it is important to put this in context, with respect to the development of the individual (individuation throughout childhood and adolescence and the emergence of self), their relationships and roles (at home, school and work, and with family, friends and colleagues). Childhood adversity can be a key pathoplastic factor—that determines how MDD manifests and how it is optimally managed. Therefore, a sensitively obtained developmental history is essential during assessment. The detailed components of taking a clinical history are shown in Figure 2.

Making sense of depression is critical. Understanding the nature of the illness, how it has emerged and how it can be best treated, is valuable for patient engagement and important for ensuring optimal outcomes. Further, it is pivotal in devising a comprehensive and effective management plan. Once a clear clinical picture of the current depressive episode and its clinical context is formed, it is necessary to consider the degree to which the aetiology and pathogenesis of the depressive disorder is driven by biological and/or psychological factors in combination with personal, social and

[a]For example, double depression refers to the occurrence of an episode of depression (major depressive episode) against a background of chronic depression (persistent depressive disorder).

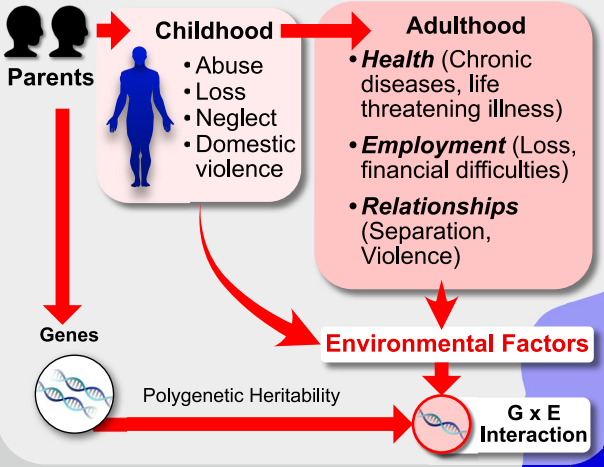
[b]Recovery means that the person is essentially back to their usual self and is no longer in need of treatment to keep any symptoms at bay. However, the person may well be on treatment if the effect of therapy is largely prophylactic/preventative.

MAJOR DEPRESSION

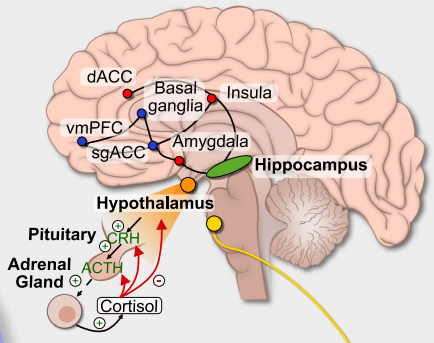
Facts

- 1 in 5 people experience major depression in their lifetime
- Major depression is twice as common in women than in men
- The illness typically emerges during the second decade of life
- 40% of patients with major depression experience their first episode by age 20

Genetic and Environmental Causes



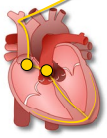
Neurobiology



- Altered emotional processing
- Hippocampal changes
- Stress-axis dysfunction

The Heart

- ↓ Parasympathetic Tone
- ↑ Risk of cardiovascular and metabolic disease risk
- ↑ Sympathetic Activation



Symptoms

Subjective

- Fatigue or loss of energy
- Worthlessness
- Guilt
- Suicidal ideation

- Depressed mood
- Anhedonia
- Impaired thinking

- Δ Appetite &/or weight
- Δ Sleep
- Δ Psychomotor activity
- Suicide attempt

Objective

Pathogenesis

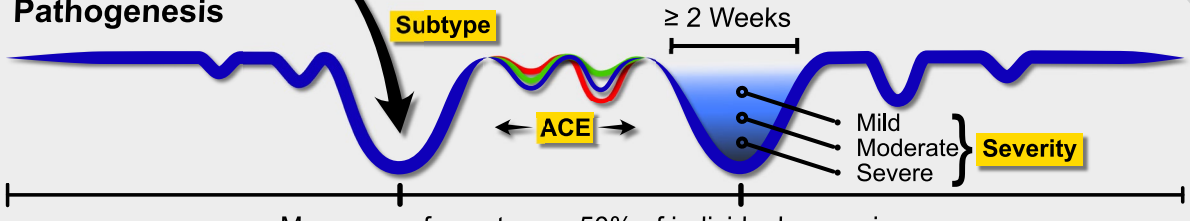


FIGURE 1 Summary of Major Depression. This figure provides key information regarding major depression. It shows the genetic and environmental causes of major depression and illustrates its neurobiological underpinnings. It displays the typical symptoms of major depression arranged along a spectrum indicating whether they can be observed objectively or need to be elicited subjectively. Note, some symptoms lend themselves to both kinds of inquiry. When grouped into a syndrome, these symptoms may reflect a particular subtype. The symptoms of depression can also be grouped according to the ACE model or rated in terms of severity. The graph at the bottom of the figure illustrates how depression typically emerges and takes hold early in life—often developing a recurrent pattern in which episodes of illness last a minimum of two weeks. [Colour figure can be viewed at wileyonlinelibrary.com]

lifestyle determinants. This will inform optimal treatment strategies, and in what order these should be implemented. Clearly, the urgency to treat the current symptoms is a critical factor, and this alone may determine initial management. For example, an acutely suicidal patient may require an immediate place of safety, and a patient who has not been drinking or eating is likely to need urgent medical review and may need immediate treatment with electroconvulsive therapy (ECT).

However, in most cases, and especially where there are many psychosocial contributory factors to the depressive illness, the initial steps of management should involve what we have described in these guidelines as *Actions*. It is important to note that *Actions* do not involve pharmacotherapy. Instead, treatment with medications is regarded as optional and is considered under *Choices* and *Alternatives*.

In many cases, changes to lifestyle, the removal of stressors (e.g. those associated with the workplace) and evidence-based psychological interventions (see below) alongside psychoeducation, will be sufficient to manage uncomplicated depressive symptoms. Nevertheless, these patients should be kept under review and psychiatrically reassessed periodically—as this helps mitigate the risk of depressive episodes recurring. This is because episodes of illness that are amenable to psychosocial treatments, early in the course of the illness, may give way to episodes that subsequently require pharmacotherapy and physical interventions to effect optimal clinical outcomes. In other words, depressive disorders by their very nature are recurrent, and therefore are likely to re-present. Furthermore, in many instances the illness may evolve, both in terms of frequency and severity of symptoms, and therefore requires increasingly more complex management.

In patients where pharmacotherapy is deemed necessary from the outset, because of patient preference or symptom severity, it is important to ensure that the necessary *Actions* have been undertaken. This is because it has been shown that the implementation of psychological therapies alongside pharmacotherapy enhances outcomes, and because adverse social and lifestyle factors often maintain depression. Furthermore, many of the *Actions* are likely to optimise the pharmacotherapeutic response and therefore it is essential that they are given full consideration at the outset of management and subsequently maintained throughout. Integrated developmentally appropriate biopsychosocial care—including healthy lifestyle and culturally sensitive practice—is the

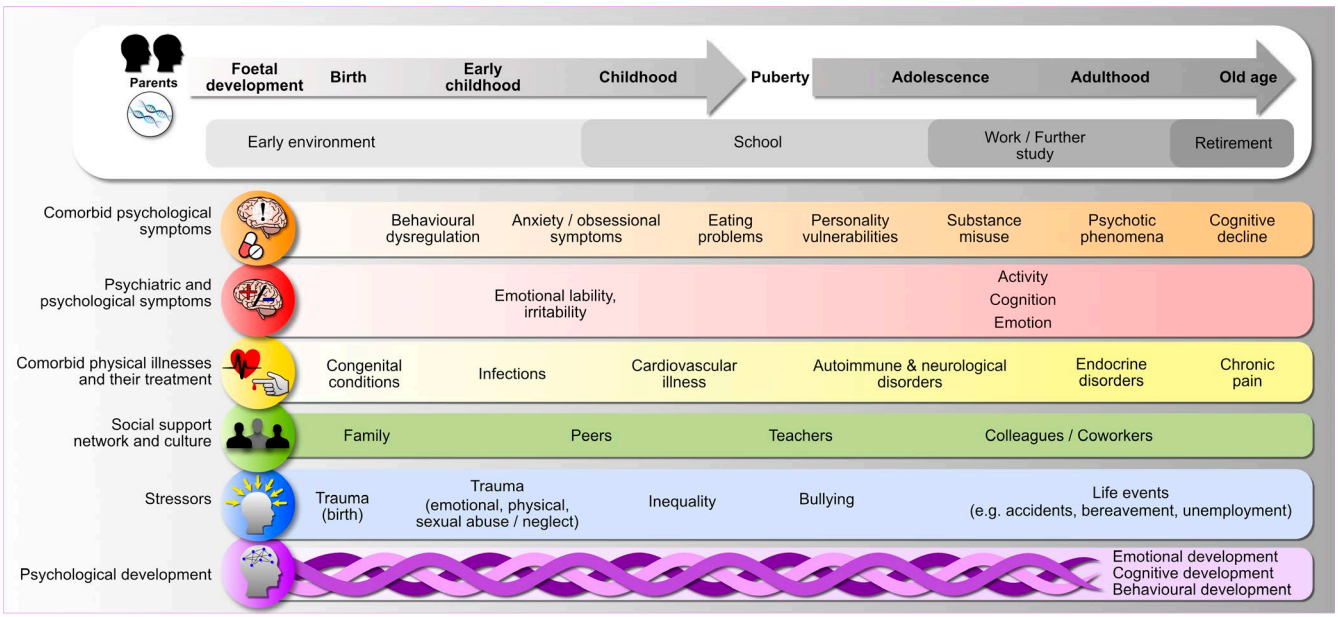


FIGURE 2 A framework for assessing the clinical factors that contribute to depression. The growth and development of an individual is depicted at the top of the figure and this 'life-line' provides a timeframe for changes across a number of domains. The domains are shown on the left and within these key aspects that should be considered and assessed are depicted according to stage of life. This then provides a framework for eliciting the clinical factors that can putatively contribute to the development and maintenance of depression. [Colour figure can be viewed at wileyonlinelibrary.com]

optimal high-level conceptual framework to achieve best care (Figure 3).

7 | ACTIONS

In the management of depression, *Actions* can be broadly thought of as developing good habits, providing knowledge, ensuring accurate measurement and supporting development of new coping skills. The details of various *Actions* are outlined in Figure 4. Amongst the many actions that are mandated, we here focus on evidence-based psychological interventions, as these require delivery by trained clinicians, typically psychiatrists, psychologists and primary care physicians (general practitioners) with training in psychological therapies.

7.1 | Psychological treatments

A core group of evidence-based psychological treatments have meta-analytic support for acute MDD,[27] with emerging evidence of longer-term benefits.[28] Several therapies (CBT, IPT, Problem-solving therapy, Behavioural activation therapy, Nondirective supportive therapy and Short-term psychodynamic therapy) have now shown superiority in comparison to wait-list control in at least 10 RCTs, notwithstanding consensus that wait-list controls can be a nocebo condition and risk spurious positive findings.[29] Nevertheless, CBT and IPT remain the primary recommended approaches for acute MDD because of their frequency of investigation, the use of manualised approaches and prominence in evidence-informed training programs. In delivering the evidence-based psychotherapies, we underscore the importance of a clinical stance of 'flexibility within fidelity': and while neither eclectic practice nor a mechanistic application of a treatment protocol are encouraged, it is recognised that at times these approaches may be necessary.[30] Furthermore, results from a recent meta-analysis also indicate that psychological therapies for depression may have differential effects across specific symptoms of depression when compared to antidepressant treatment.[31]

Reflecting the rapidly changing delivery landscape, the 2020 RANZCP guidelines include detailed consideration of digital delivery of psychological therapies (interventions offered on computer, tablet or smart phone). Existing evidence suggests that digitally delivered interventions (again, dCBT having the strongest support) may have equivalent efficacy to in-person treatment for MDD but with significant cost benefits, notwithstanding that many dCBT trials have wait-list controls (see above). Still, improved access to digital delivery has been realised in 2020 through government initiatives triggered by COVID-19 restrictions—especially in remote areas or where there is limited access to mental health professionals. In addition, because of accessibility, digital interventions are emerging as an important public health strategy that can deliver universal interventions for those that may have emergent symptoms (perhaps assessed in an online platform), but have not yet reached criteria for disorder. Nevertheless, clinically, in-person treatment remains critical and is

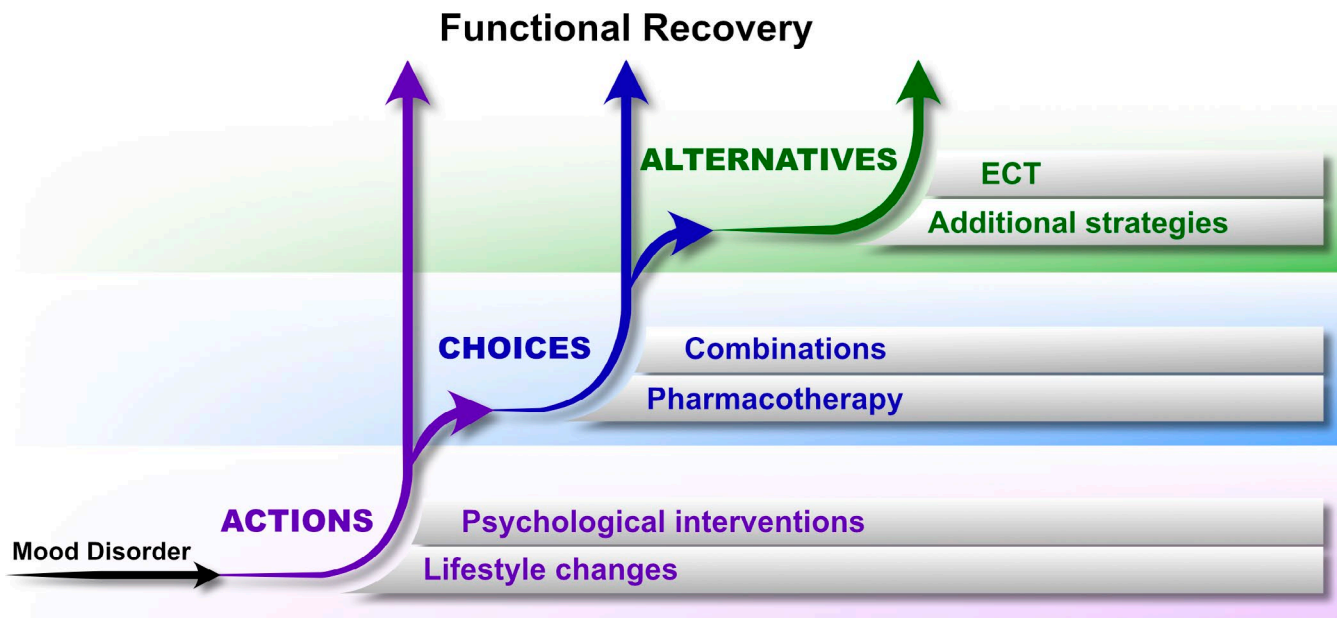


FIGURE 3 The Actions, Choices and Alternatives framework for the management of mood disorders. This framework includes three components. (1) *Actions*—form the basic foundation of management and should be instituted whenever possible. They include lifestyle changes and psychological interventions. (2) *Choices*—involve those pharmacotherapeutic options that are recommended and should be trialled initially. They can also be used as part of more complex regimens involving combinations and alternative treatment strategies. (3) *Alternatives*—include complex medication strategies and physical treatments such as ECT. It is important to note that functional recovery can be achieved at any point in this process, and the aim should be to achieve this as quickly and effectively as possible. [Colour figure can be viewed at wileyonlinelibrary.com]

FIGURE 4 Actions for the management of depression. Where possible, *Actions* should be undertaken to facilitate functional recovery. There are three groups of *Actions*. The first group are those the patient needs to *institute*, such as *lifestyle changes*. These include sleep hygiene, maintaining a healthy diet and taking regular exercise. The second group of *Actions* are those the patient needs to *address* as a priority—although they may require assistance—such as limiting drinking and the cessation of smoking. These habits adversely impact mood and may interfere with treatments, especially medications. However, it is important to acknowledge that stopping smoking, for example, is extremely difficult and that attempts to do so during depression may exacerbate symptoms of the illness, and therefore, engagement in a suitable program of withdrawal may need to take place once a person has recovered. The third group of *Actions* are those that need to be *implemented*. These include *psychoeducation* and *psychological treatment*. In addition, it is important to consider the social needs of the individual, and how these are impacting their depressive illness, and assist with these if possible (e.g. referring to social worker). Finally, the *assessment* (measurement) of clinical symptoms, and especially those related to any risks, and a structural appraisal of overall outcome are vital. [Colour figure can be viewed at wileyonlinelibrary.com]

often preferred by both patients and clinicians, highlighting the different strengths and weaknesses of in-person versus digital delivery for different patients and different phases of management.

Digital delivery may be suboptimal for managing risks around complex and changing presentations of pathology. Consequently, it is recommended that while digital delivery may be as effective as in-person treatment all other things being equal, at key points in treatment (baseline assessments, change of medication, life events, changing symptoms or risk), the cost-benefit analysis currently favours in-person appointments where feasible. However, a more nuanced understanding of the optimal blending of digital and in-person management is rapidly emerging, and online treatment is clearly advantageous in terms of access and privacy/stigma.

The MDcpg[2020] marks an important shift in the positioning of psychological interventions for MDD. The earlier guidelines[2] presented severity as a key factor in choosing between psychological versus medication treatment, but evidence review failed to support this simple bifurcation. Direct tests have not supported the hypothesis that psychological treatments are always less effective for more severe presentations of depression, and the notion that some depressive presentations are relatively unresponsive to psychological treatment has only limited empirical support. Finally, there is robust meta-analytic support for the conclusion that for all severities of depression the most effective treatment is a combination of psychological interventions and pharmacotherapy—although it is important to note that this comes largely from studies of ambulatory patients and thus may not apply to the very severe presentations seen in tertiary care.[32] Thus, given that psychological interventions are preferred by many patients, have a generally (albeit not absolutely) positive side-effect profile, likely secondary benefits in terms of resilience-building post treatment and the recent accessibility improvements of digital delivery, it is recommended that structured psychological treatment is foundational in the treatment of all depressive presentations.

In sum, the 2020 Guidelines move away from polarising psychological and medication treatments, and represent an advance towards an integrated stance based on understanding the strengths and weaknesses of various approaches.

8 | CHOICES

If the *Actions* outlined above prove to be insufficient to achieve remission, and the patient is amenable to pharmacotherapy, then an antidepressant should be prescribed. In some instances, an antidepressant may be prescribed from the outset, for example, where prior experience has shown that medication is needed. Therefore, prior to commencing pharmacotherapy, it is important to have determined whether the patient has had previous treatment (see Diagnostic and management formulation of depression).

When selecting an antidepressant, there are two main considerations: *efficacy* and *tolerability* (note, *effectiveness* is a combination of the two, and it is *not* synonymous with efficacy).

8.1 | Efficacy

In terms of efficacy, while all antidepressants have been shown to be better than placebo[c], clinically there is also a gradation of effect amongst various antidepressants. However, the differential activity of antidepressants is derived from a mix of naturalistic experience and empirical studies and, importantly, there are few direct head-to-head studies of antidepressant agents to provide definitive evidence to shape preference. Generally speaking, and based on clinical experience, medications with a broader spectrum of actions, such as the tricyclics (e.g. amitriptyline), appear to be clinically more efficacious, while those that are more selective tend to be less so. By the same token these agents with a broad mechanism of action, generally have a greater likelihood of producing side effects that can potentially impact compliance and effectiveness. Efficacy is also dependent on depression severity, subtype and the particular clinical profile of symptoms the person is experiencing. Therefore, although there is a modest hierarchy with respect to efficacy, this should not be the principal determinant of antidepressant selection.

8.2 | Tolerability

Tolerability is as important as efficacy, and medication adherence is critical from the outset. Therefore, when commencing antidepressant therapy, in addition to being advised of potential side-effects, patients should also be asked to be vigilant and monitor not only their symptoms, but also how they react to the medication more generally. If side effects occur, they should report these promptly, rather than stopping medication (unless these are intolerable), and seek assistance and review, as soon as possible. In practice, it is useful to have a follow-up appointment within 2 weeks of commencing medication. This allows for a detailed appraisal of response and a general review of overall functioning. Most side effects will manifest within the first week of treatment by which time steady state serum levels of most antidepressants will have been reached. A 'start low' and 'go slow' approach to dosing can be adopted for patients of advanced age, or those with a history of poor medication tolerance, or those apprehensive about taking medication.

Common side-effects that patients find troubling include gastrointestinal symptoms such as nausea and diarrhoea, sexual dysfunction, sedation, weight gain, anxiety, over-stimulation and agitation. Where patients have been previously prescribed antidepressants, it is important to determine their responsivity and side-effect profile noting the side-effects that they have experienced with previous agents (see Figure 5). Where a previous antidepressant has been well tolerated and effective this should be re-instated at the previously effective dose. It is important to consider any potential interactions with other medications the patient may be taking and to modify choice accordingly. On occasion, suicide risk may also need to be factored into prescription choice as some agents are potentially more lethal than others in overdose (e.g. tricyclic antidepressants).

8.3 | Selecting an antidepressant

To tailor the actions of an antidepressant to the clinical profile of a patient, it is important to understand the pharmacological actions of different medications. Figure 6 illustrates the seven molecules that are recommended as *Choice* agents. Each of these has a slightly different pharmacological profile and thus a unique effect, both in terms of efficacy (see Table 1) against specific symptoms and in terms of tolerability, with different side-effects (see Figure 5). Collectively, the seven agents provide a broad range of mechanisms of action. A notable omission is that of monoaminoxidase inhibition, which has a broad spectrum of efficacy but because of its interactions, has been positioned as an *Alternative* antidepressant, rather than a *Choice* agent.

9 | ALTERNATIVES

There are now nearly 30 molecules that have antidepressant properties and have an indication for the treatment of depression, in addition to which there are many agents that have adjunctive roles in this regard. Therefore, there are multiple choices and options available. However, in many cases, these interventions are either ineffective or insufficient on their own, and this means that additional, *Alternative* strategies have to be employed. Chief amongst these is the combination of the types of treatment, and as has already been emphasised, the combination of psychological interventions with pharmacotherapy is essential where possible. Ideally, this should be delivered within the context of having instituted many of the lifestyle and habit-transforming *Actions*.

Nevertheless, it is quite possible that these steps have not achieved a satisfactory response or remission/recovery, and so *Alternatives* are necessary. For this, we advocate pursuing a number of strategies depicted in Figure 7 and summarised with respect to medication in the acronym *MIDAS*.

[c]Note: superiority over placebo is required for regulatory approval.

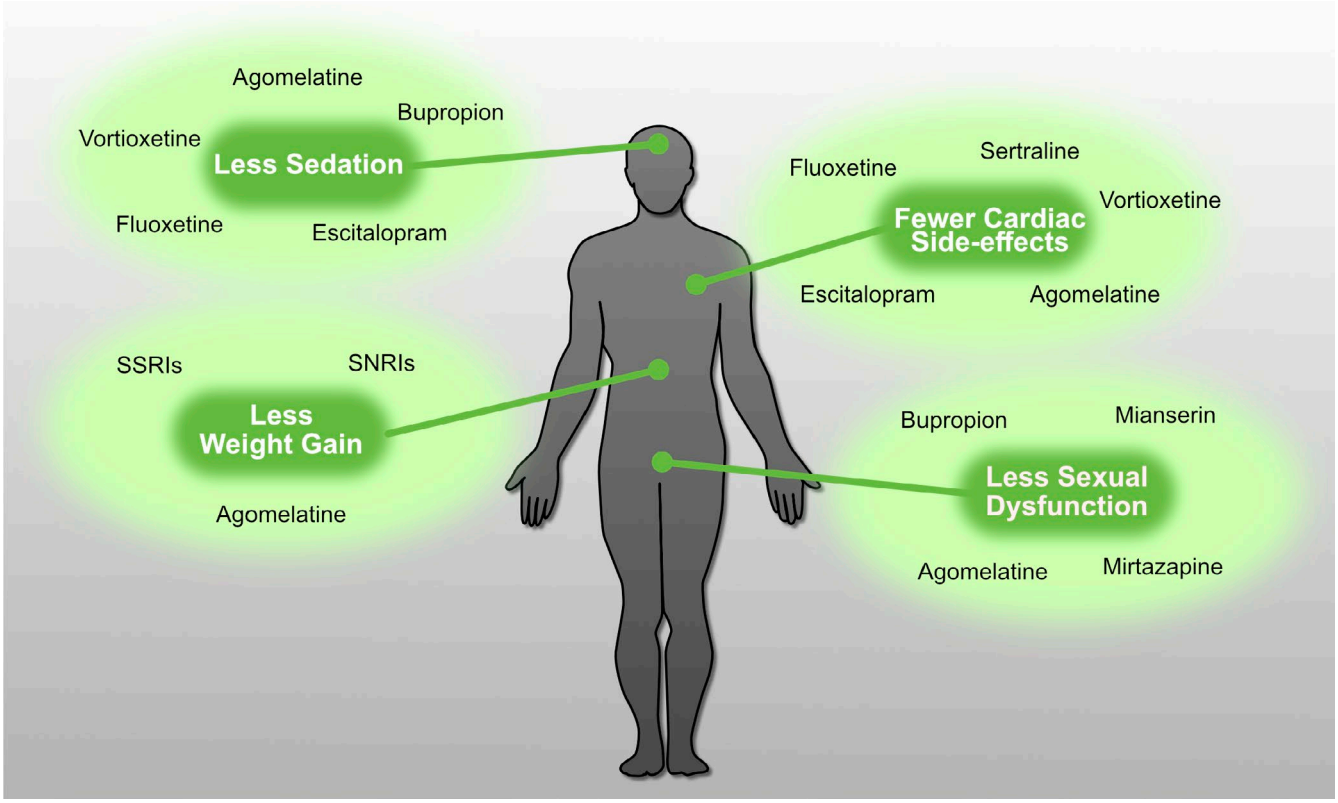


FIGURE 5 Selecting antidepressants to minimise side-effects. Treatment with antidepressant medication is potentially associated with many side effects. Fortunately, the majority of these are mild and transient, but in some instances, side-effects can be severe and debilitating. In practice, the key problem with respect to poor antidepressant tolerability is that patients are unlikely to complete a course of antidepressant treatment if they are experiencing significant side-effects. The figure shows four groups of antidepressants (in no particular order) relatively less likely to generate the common side effects of sedation, weight gain, cardiac and sexual dysfunction. It is important to note that these side-effects *can* occur with these agents, but are less likely to occur as compared to other antidepressants. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Pharmacological treatment based on clinical profile

Key/prominent symptom(s)	Antidepressant
Anxiety	Escitalopram Venlafaxine
Cognitive difficulties (learning, memory, decision-making)	Vortioxetine
Sleep disturbances (e.g. Insomnia)	Agomelatine Mirtazapine
Fatigue	Bupropion
Pain	Amitriptyline
Melancholia (psychomotor slowing, diurnal mood variation)	Amitriptyline Venlafaxine

Note: Table 1 shows *Choice* antidepressants that may be suitable for the treatment of depression where certain symptoms are particularly prominent. Note, that in addition it is important to consider overall efficacy and tolerability as well as depressive subtype and severity, past treatment history and responsivity, along with patient preference.

9.1 | MIDAS

When considering alternative strategies with respect to medication (M), it is assumed that a *Choice* agent has been prescribed and either a partial, or no response, has been achieved. In either case, but especially if there is a partial response, an increase in dose (ID) should be considered. Most antidepressants have a dose range, and for some medications this can be extremely broad (e.g. venlafaxine has a potential ten-fold increase from 37.5 mg to 375 mg). This will overcome any pharmacokinetic limitations that may have prevented sufficient medication reaching its targets within the brain (bioavailability). In some cases, there may also be a pharmacodynamic benefit (e.g. increasing receptor binding). Persisting with this strategy also ensures that this option has been optimised before pursuing a different strategy. If, with an increase in dose there is still only a partial response after a few weeks, or a previous partial response has not been sustained or amplified, then augmentation (A) should be considered. It is important to note that if at this stage there has been no response whatsoever, then augmentation is less likely to help, unless the agent that is administered has an additional synergistic antidepressant effect. This may be the case for example, with lithium or some atypical antipsychotics, but it is important to bear in mind that these effects are modest, and may be insufficient to enhance the primary antidepressant effect. Hence, it is our expert consensus that augmentation is most useful where there has already been a partial response, either initially or through an increase in dose and the patient is accepting of this strategy.

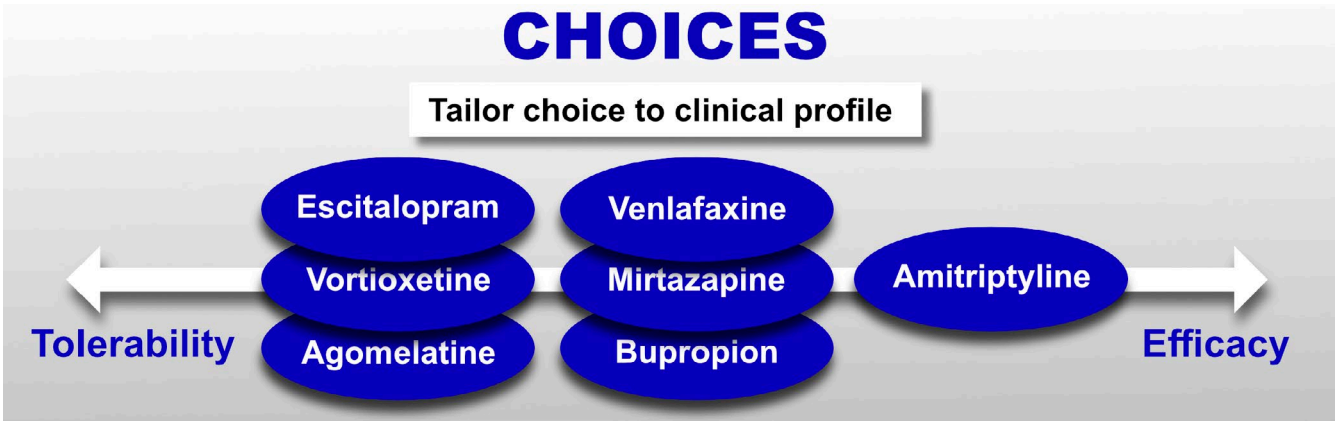


FIGURE 6 Pharmacotherapy Choices for the management of depression. The *Choice* antidepressants each have different mechanisms of action. Broadly, all have actions on monoaminergic systems, with some medications having additional effects (e.g. agomelatine on melatonergic receptors and tricyclic antidepressants on cholinergic receptors). The different receptor-binding profile of each antidepressant means that there is some separation in terms of clinical effects—both efficacy and tolerability. At the same time, it is important to note that there is 'cross-talk' between the various systems, meaning that there is some convergence of therapeutic effects. Knowledge of the different mechanisms of action is important as it provides a basis for understanding the different clinical effects and profiles of these medications (see MDcpg[2020]). The seven *Choice* antidepressants are depicted according to their relative efficacy and tolerability. Choice should be further refined according to clinical profile (see Table 1), depressive subtype and severity, past treatment history and responsivity and patient preference. [Colour figure can be viewed at wileyonlinelibrary.com]

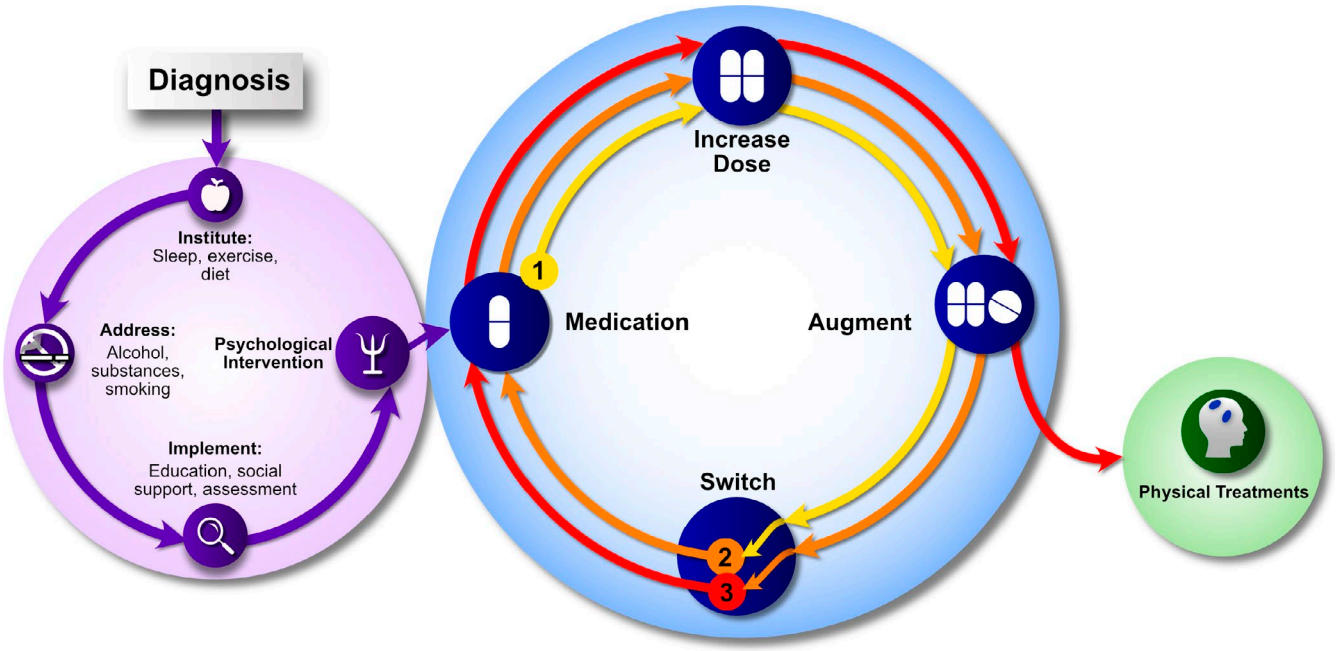


FIGURE 7 MIDAS Framework. The figure shows the management of depression commencing following diagnosis and clinical formulation. Initial *Actions* are instituted, addressed and implemented and psychological intervention provided. If necessary, pharmacotherapy is prescribed either concurrently or after psychological therapy has been established. *Medication* is selected to suit the clinical profile of the depressive presentation as per the *Choices* available and according to effectiveness. The first antidepressant (1) is then prescribed at the optimal dose and this can be increased (*Increase Dose*, *ID*) if necessary. If this is insufficient then *Augmentation* can be considered in which an augmenting agent such as lithium can be added to the antidepressant. This is especially useful if there is an antidepressant response already (even if only partial). However, if this strategy is ineffective then the antidepressant needs to be substituted. *Switching* the antidepressant should ideally involve shifting to another class altogether (e.g. a different *Choice* antidepressant medication), but switching within class is acceptable if the main reason for doing so is that the initial medication was not taken as prescribed (e.g. because of side effects or poor adherence). The MIDAS cycle should be repeated for as many of the *Choice* antidepressants as possible (and at least 3) before considering a physical intervention such as ECT, although the latter may be indicated much earlier in some cases, for example where depression is marked by psychotic symptoms. [Colour figure can be viewed at wileyonlinelibrary.com]

For the purposes of augmentation, lithium has been shown to be particularly effective in the context of recurrent depressive episodes, and its usual therapeutic dosing is appropriate (levels of 0.6–0.8 mmol/L), although there is some evidence to suggest that even lower plasma levels may also be of help (0.4 mmol/L).[33-35] The effect of lithium augmentation is likely to be evident relatively quickly, and so if there is no significant improvement within two weeks after a therapeutic level of lithium has been achieved, then lithium should be withdrawn.

Alternative augmentation agents include some atypical antipsychotics (e.g. aripiprazole).[36] These should not generally be used long-term because of potential side-effects (e.g. akathisia in the short-term and weight gain, metabolic disruption and tardive dyskinesia in the long-term).[37,38] Again, it is important to note that the augmenting agent is acting upon the primary antidepressant effect of the initial antidepressant prescribed and so if one augmentation strategy is ineffective, another augmenting agent can be trialled.[39] However, if augmentation as a strategy is ineffective, then all the medications that have been prescribed as part of the strategy should be removed when switching to another medication.[40] Indeed, switching (S) is the next *Alternative*, once an increase in dose and/or augmentation has been trialled.

At this point, it is necessary to emphasise that switching within classes of antidepressants can sometimes be effective, as most agents within a class have slightly different specificities of action; as shown in the STAR*D study.[41] However, generally speaking, switching within class should be reserved for intolerability, such as when side-effects have precluded an adequate trial of the antidepressant. For example, if soon after a selective serotonin reuptake inhibitor (SSRI) has been prescribed, it has had to be stopped because of an intolerable side-effect (e.g. sustained nausea and vomiting), treatment can be switched to another, better-tolerated SSRI. However, if the reason for switching is primarily a lack of efficacy, especially after increasing dose and augmenting, then there is possibly more merit in pursuing a different mechanism of action and trialling a medication from a different class altogether.

Generally speaking, as per Figure 6, agents with a broader spectrum of action generally have greater efficacy but are also more likely to produce side-effects. Once an alternative antidepressant has been decided upon, and treatment is switched, the MIDAS cycle can once again be repeated—increasing the dose and augmenting as necessary. Given the many classes of antidepressants that are available, and the many agents within some of these classes, the MIDAS cycle can be repeated many times. The STAR*D study clearly underscored the importance of perseverance and the need for trialling more than one medication, indicating that for a significant proportion of depressed patients, two, three, four and sometimes many more antidepressants are necessary in sequence.[41] Notably, recent data from the world mental health survey suggest that 93.9% of patients perceived therapeutic benefit from trying up to 10 trials of treatment, highlighting the need for persistence.[42] We therefore advocate the same, and in fact suggest that a minimum of three cycles should be trialled, and in some instances, several more can be considered - unless switching to a physical treatment such as ECT is indicated or clearly necessary.

It is important in the process of titrating doses and withdrawing medications, when switching from one agent to another, to be aware of side-effects, interactions and withdrawal symptoms and it may be helpful at this point to seek specialist review from a psychiatrist.

9.2 | Physical treatments

Many kinds of additional physical treatments have been developed and trialled for the treatment of depression, but none is as effective as ECT, and in most cases, because of indication, access and cost, ECT is the best and most suitable physical treatment option. Figure 8 shows progression through a number of variations of ECT, in which the stimulus intensity and electrode placement is altered. Here again, it is evident that with increasing efficacy, there is the increasing likelihood of transient cognitive side-effects and therefore, where possible, brief or ultra-brief pulse unilateral ECT should be trialled first.[43,44] However, in some instances, bifrontal or bitemporal ECT is necessary. This should be considered earlier where there are clear features of melancholic depression such as psychomotor retardation and psychotic features, such as mood-congruent delusions and hallucinations.[45,46] ECT is also first-line for the treatment of catatonia in the context of a mood disorder and can also be administered as a matter of urgency where a patient is refusing oral medication and there is an urgent need for treatment because of inanition and dehydration.[45,46] It is also important to note that ECT is safe in pregnancy,[47,48] and therefore in some instances, it may be the preferred option.

Recommendation Box 1. Management of acute MDD		Grade
1.1	Clinicians should assist patients to overcome well-recognised barriers to accessing psychological interventions (e.g. via providing information about online psychological treatments, advice about local therapists and the rationale for developing skills to prevent relapse)*	CBR
1.2	Psychological interventions should only be delivered by clinicians trained in the relevant evidence-based approach	EBR I
1.3	One of the evidence-based psychological interventions should be offered as foundational care (Action) to all patients (the most extensive evidence is for CBT and IPT, but a range of interventions have strong evidentiary support)	EBR I
1.4	Combined psychological intervention and antidepressant medication is more effective than either type of intervention alone	EBR I

* Two contextual factors regarding psychological treatments are important in the management of acute MDD: patients generally

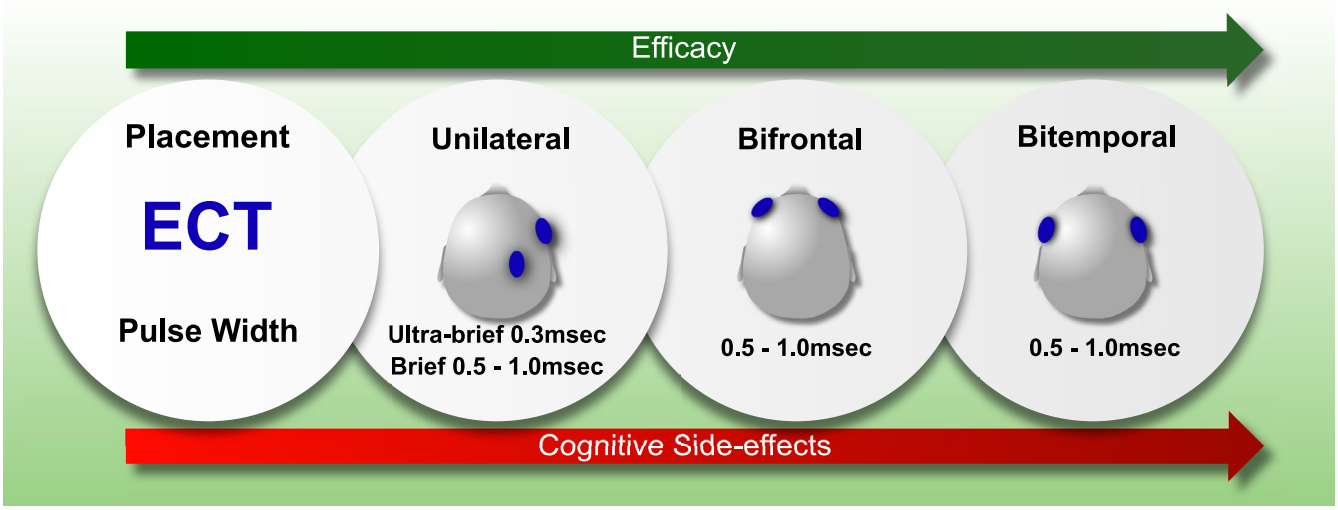


FIGURE 8 ECT in depression. ECT can be applied unilaterally or bilaterally, over frontal and temporal regions (bifrontal and bitemporal respectively). The pulse-width can be varied from 0.3 to 1.0 msec, allowing different amounts of stimulation to be applied. Efficacy increases from unilateral to bilateral ECT and with an increase in pulse-width from ultra-brief to brief. However, with increasing efficacy there is an increase in the likelihood of cognitive side-effects. [Colour figure can be viewed at wileyonlinelibrary.com]

prefer psychological intervention over antidepressant medication; and psychological interventions are becoming more accessible due to increased numbers of trained clinicians, online self-management programs and telehealth platforms.

10 | MAINTENANCE TREATMENT

For most episodes of depression, one or other of the many treatments available (lifestyle, psychological, pharmacological and physical) is likely to be effective. It is also important to remember however, that episodes of depression are intrinsically recurrent, and therefore periods of acute illness will often remit spontaneously. But even in these instances, persisting with treatment is important as it ensures continuing engagement of the individual and allows for the ongoing provision of care. In this regard, it is important not to limit the focus of management to the treatment of an acute episode of depression. The disorder's recurrent course, the persistence of subsyndromal symptoms and increased suicide risk suggest that continued monitoring is warranted. Indeed, it is during the maintenance phase of management that the focus of clinicians can fully shift to building resilience against future episodes and moving towards quality-of-life enhancement.

10.1 | Pharmacotherapy

The aim of continuing treatment is to prevent future episodes of depression, i.e. to provide prophylaxis. Therefore, following a depressive episode, we recommend maintaining antidepressant treatment for at least six months, and up to one year (see meta-analysis),[49] and especially if there have been several episodes of illness.[50] Beyond one year there is modest evidence for continuing antidepressant therapy that suggests those receiving antidepressant treatment beyond 12 months (NNT 3.8 CI 3.3–4.6) have significantly fewer reoccurrences.[51] However, there is little data to support continuing antidepressant treatment beyond 2 years, and there is no consistent evidence in this regard favouring any antidepressant class. Thus, at present, it is recommended that the antidepressant dose used during maintenance therapy should remain the same as that used in acute therapy.

10.2 | Psychological treatments

A comprehensive systematic review has supported earlier recommendations that CBT is effective in protecting against relapse, and that mindfulness-based cognitive therapy is effective in patients with three or more episodes.[52] As in the management of acute depression, there is evidence that, combined psychological intervention and pharmacotherapy may have the strongest prophylactic effect.[53]

11 | TREATMENT RESPONSIVITY

In recent years, there has been a resurgence of interest in both defining and understanding the lack of response to treatments in depression. Traditionally, this has been described as 'treatment-resistant depression' (TRD), and less nihilistic terminology (such as difficult-to-treat depression; DTD) has been sought.[54] However, these concepts all emphasise lack of response, and position management with a focus on poor outcomes and the likelihood of failing to respond. This is obviously damaging for the individual but is also restrictive for clinicians who then assume that the underlying depression is

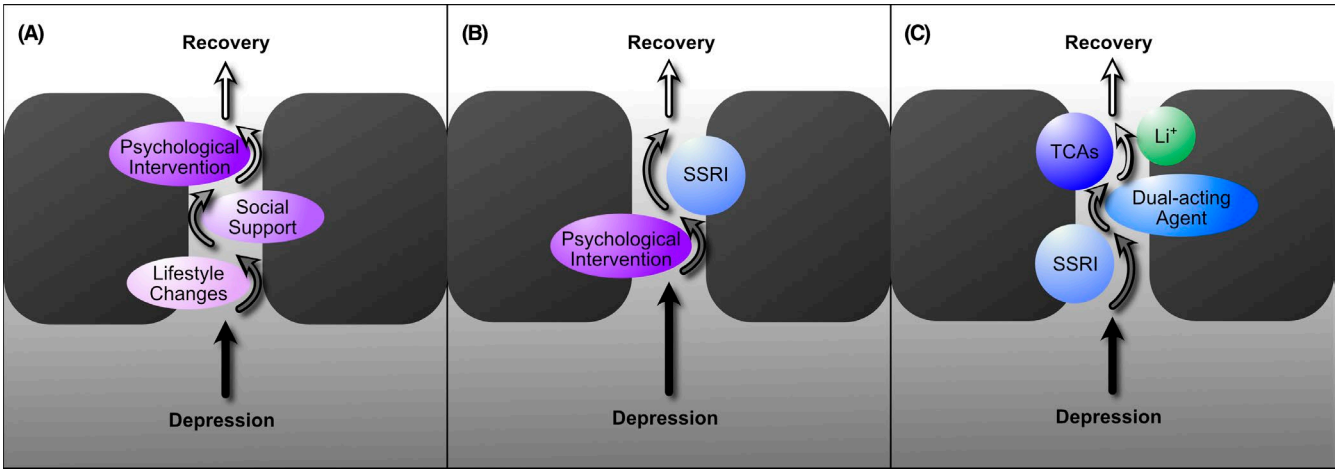


FIGURE 9 Responsivity Paradigm. The schematic above shows three channels that represent typical examples of pathways from depression to recovery. Each of the figures depicts different sets of treatments being used individually in sequence or in combination to affect change. (A) Combination of lifestyle changes, social support and psychological interventions (such as CBT) to facilitate recovery from depression. (B) Combination of psychological intervention and an SSRI to achieve recovery. (C) Sequencing of agents. First, an SSRI may be prescribed, but this only achieves a partial response and therefore it is suited to a dual-acting agent and then further supplanted by a broad-spectrum antidepressant such as a tricyclic (TCA). However, in this instance further treatment is necessary and an augmentation strategy (addition of lithium) is implemented to achieve recovery. [Colour figure can be viewed at wileyonlinelibrary.com]

likely to be treatment-non-responsive. This negative perspective also frames the individual as having contributed to the problem and raises the complex role of personality factors, which although potentially contributory, are not necessarily the main reason as to why a satisfactory response has not been achieved. We recommend an alternative framing—the *responsivity paradigm*—to address this type of presentation.

A common cause of unsatisfactory response to any depression treatment, is a lack of adherence and pursuit of the treatment as prescribed.[55] This applies to lifestyle advice, psychological interventions and pharmacotherapy. Many of the *Actions*, such as diet and exercise, are challenging and are difficult for everyone irrespective of whether they are suffering from depression. Psychological interventions often require motivation, structure and organisation, and again it is understandable that patients may not fully engage with treatment recommendations. Pharmacotherapy can sometimes be seen as stigmatising and may also be regarded as unnecessary or dependence-inducing, and so patients will again often (and somewhat understandably) not take medication as prescribed—changing doses for example, and stopping and starting treatment as they deem appropriate.

However, setting aside these issues, even when therapy is appropriately prescribed and adhered to, and suitable strategies have been implemented, a satisfactory response may not be forthcoming. In the *responsivity paradigm*, we have advised that this should be acknowledged at the outset, and that it should be accepted that there are a number of different *channels* (pathways) of treatment that can be pursued and that it is not known at the start of treatment which of these is most likely to be effective. Hence, there is an element of having to trial different strategies until the appropriate strategy is found. In practice, this process can be optimised by characterising the depression and formulating the illness thoroughly (see previous).

Having this discussion at the beginning of management allows the provision of a series of strategies that encompass different kinds of treatments. It makes it clear from the outset, both for the patient and for the clinician, that the task ahead may take time. Counterintuitively, this approach also injects a sense of urgency and avoids the investment of too much importance in any one single strategy. We therefore advocate regular review and revision of the treatment strategy being employed, and discarding a particular pathway or channel if it is not yielding results. This can be done in consultation with patients so that treatments and treatment targets can be collaboratively agreed upon.[56]

Reviewing the diagnosis and formulation regularly will also open many channels of responsivity, and as treatment progresses, different strategies can be trialled. The examples shown in Figure 9 make it clear that in some instances, more than one kind of therapy may be needed, and that in some cases, initial treatment may 'prime' the effects of later treatments, thus facilitating overall efficacy. The key advantage of this approach is that the assumption is not one of a lack of response per se, but one of knowing that a particular channel of response will work, and a particular strategy will be effective. This provides a positive mindset, both for the patient and clinician, and avoids repeated disappointments and discussions as to lack of response. Instead, clinical improvement is monitored and discussed, and versatility is introduced into management. The responsivity paradigm thus dispenses the need to describe patients as having treatment-resistant depression or difficult-to-treat depression, and appropriately raises the bar for this designation. This is of critical importance because TRD is increasingly being used to describe first, a supposed subtype of depression—for which there is no evidence;

and second, an indication for novel untested treatment strategies. Thus, the responsivity paradigm is our recommended approach for navigating poor response.

12 | CONCLUSIONS

Depression is a common and severely disabling psychiatric disorder, but one which is highly treatable. Its assessment and treatment require a sophisticated and layered approach to ensure patients have the best chances of achieving full functional recovery. When managed well, patients with depression can acquire skills to cope with stress and develop emotional resilience that may also mitigate the risk of future acute exacerbations. Optimally, the management of depression should be founded on actions such as psychoeducation and healthy lifestyle measures. Psychological interventions should be offered from the outset and pharmacotherapy should be integrated along with physical treatments if necessary—for patients who do not attain satisfactory outcomes with initial care. Throughout management, it is important to maintain an optimistic and response-focused outlook—to ensure all available options are adequately explored. Ultimately, most cases of depression are eminently treatable and with appropriate treatment, meaningful functional recovery can be achieved.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

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ORCID

Gin S. Malhi https://orcid.org/0000-0002-4524-9091
Erica Bell https://orcid.org/0000-0002-8483-8497
Ajeet B. Singh https://orcid.org/0000-0002-0853-7959
Michael Berk https://orcid.org/0000-0002-5554-6946
Philip Boyce https://orcid.org/0000-0002-9816-7356
Richard Bryant https://orcid.org/0000-0002-9607-819X
Michael Gitlin https://orcid.org/0000-0001-7236-9649
Amber Hamilton https://orcid.org/0000-0001-9001-4585
Philip Hazell https://orcid.org/0000-0002-8085-2996
Malcolm Hopwood https://orcid.org/0000-0001-6004-4521
Roger S. McIntyre https://orcid.org/0000-0003-4733-2523
Grace Morris https://orcid.org/0000-0003-3598-9712
Roger Mulder https://orcid.org/0000-0002-8147-5838
Richard Porter https://orcid.org/0000-0002-8695-3966
Lakshmi N. Yatham https://orcid.org/0000-0002-7405-0954
Greg Murray https://orcid.org/0000-0001-7208-5603

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