Adult depression

A step-by-step guide to treatment

JOSEPHINE ANDERSON BA, BMed(Hons), MMed, MHealthLaw, FRANZCP, Cert Child Adol Psych
VERONICA GALVEZ MB BS, MD
COLLEEN LOO MB BS(Hons), FRANZCP, MD
PHILIP B. MITCHELL AM, FASSA, MB BS, MD, FRANZCP, FRCPsych

A stepwise approach to the early detection and management of depression, guided by severity of presentation and treatment response, can ensure timely access to treatment. Evidence-based treatments range from e-mental health apps, psychological therapy and medication to neurostimulation.

KEY POINTS

- A stepwise approach to evidence-based primary mental health care promotes early detection of patients with depression.
- Early detection by GPs encourages more timely access to evidence-based treatments, including easily accessed and destigmatising e-mental health interventions.
- Given the overall similarities in efficacy of antidepressants, the most important considerations when initiating pharmacotherapy are tolerability and safety, although some patients uniquely respond to some medicines and not others.
- For patients with difficult-to-treat depression, an algorithmic management approach with steps that include increasing the antidepressant dose, switching antidepressants, augmenting with a nonantidepressant treatment and combining antidepressants improves the chance of patient recovery.
- Neurostimulatory treatments such as electroconvulsive therapy and repetitive transcranial magnetic stimulation have an expanding role in the evidence-based treatment of severe depression.

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Dr Anderson is Conjoint Associate Professor in the School of Psychiatry at the University of New South Wales; and Clinical Director of the Black Dog Institute, Sydney. Dr Galvez is Visiting Psychiatrist and Clinical Research Officer in the School of Psychiatry at the University of New South Wales and SyNC (Sydney Neurostimulation Centre), Black Dog Institute, Sydney. Professor Loo is Professor in the School of Psychiatry at the University of New South Wales; Clinical Academic at St George Hospital; Director of SyNC; Professorial Fellow at the Black Dog Institute; and Director of ECT at Wesley Hospital, Sydney. Scientia Professor Mitchell is Head of the School of Psychiatry at the University of New South Wales; and Professorial Fellow at the Black Dog Institute, Sydney, NSW.

Major depressive disorder occurs in 5% of adults annually and has effects on quality of life equal to or greater than those of ischaemic heart disease or diabetes.[1] Around 25% of patients who present to their GPs with depressive symptoms have major depressive disorder. Nonetheless, currently around 50% of people with this severity of depression are unable to access or do not receive appropriate care.[2]

In this article, we describe a stepped care approach to the treatment of major depressive disorder in adults, with recommendations appropriate to patients who present at each level of severity. We focus on early detection and access to evidence-based e-mental health, pharmacological and physical treatments, including new therapies. Many of the resources and strategies described here have been developed at the Black Dog Institute in Sydney.

A stepped approach to care

Detecting and diagnosing major depression

Given the frequency of mental health problems in general practice, GPs may wish to screen all patients for symptomatic depression (and associated anxiety) using well validated tools such as the Patient Health Questionnaire (PHQ-9) or the Generalised Anxiety Disorder 7 (GAD 7) scale.[3-5] These are self-report scales in the public domain. They also help to distinguish mild, moderate and severe depression, with implications for treatment recommendations (see below).

In addition, the *Diagnostic and Statistical Manual of Mental Disorders,* 5th edition (*DSM-5*) describes the necessary symptoms for a diagnosis of major depressive disorder and classification of its severity, which may be mild, moderate or severe (Box 1).[6]

1. MAJOR DEPRESSIVE DISORDER: DSM-5 CRITERIA AND SEVERITY CLASSIFICATION[6]

Criteria for diagnosis

- Pervasive depressed mood or loss of interest/pleasure in usual activities together with four or more of the following symptoms, present nearly every day:
  - significant weight loss or gain or decrease in appetite
  - insomnia or hypersomnia
  - psychomotor agitation or retardation
  - fatigue or loss of energy
  - feelings of worthlessness or excessive or inappropriate guilt
  - diminished ability to think or concentrate or indecisiveness
  - recurrent thoughts of death or suicide or suicide attempts

Classification of severity

- Mild: few if any symptoms in excess of those needed to make the diagnosis and although distress may be evident, the disorder leads to only 'minor impairment in social or occupational functioning'
- Severe: the number of symptoms is substantially in excess of that required to make the diagnosis, the 'intensity of the symptoms is seriously distressing and unmanageable', and symptoms 'cause marked interference with occupational and social functioning'
- Moderate: between the extremes

Management

In the stepped care approach, patients with major depressive disorder are managed according to the severity of their depression on presention, with care being stepped up if there is not sufficient response to treatment.

Step 1: mild depression

Patients with mild depression (or mild major depressive disorder) can be observed, educated and advised regarding daily exercise, sleep hygiene and mood monitoring (the latter alone can be associated with positive changes in mood and functioning).[7,8] E-mental health interventions encourage patients to monitor their mood and note the circumstances associated with mood fluctuations. Evidenced-based examples that are available on the Internet and smart phones include:

- myCompass (free, with a pre-registration overview; www.mycompass.org.au)
- This Way Up (registration and a small fee are required; https://thiswayup.org.au).

These programs are readily accessible and destigmatising and also provide treatment modules that have proved effective for the treatment of mild to moderate depression.[9]

At subsequent visits, GPs can review mood monitoring and the treatment modules tried, providing useful springboards for

2. MAJOR DEPRESSION WITH ATYPICAL FEATURES

- Symptoms include:
  - presence of mood reactivity and lifting of mood in the context of pleasant events
  - hypersomnia rather than early morning wakening
  - increased appetite or weight gain rather than anorexia and weight loss
  - a subjective sense of heavy leaden feelings in the arms or legs rather than observed psychomotor agitation or retardation
- Patients also often exhibit a long-standing pattern of sensitivity to interpersonal rejection that results in significant social or occupational impairment
- Depression can be mild, moderate or severe

discussion. Reviewing patients at least fortnightly encourages adherence and allows monitoring of improvement, generally evident within four weeks.

RACGP-accredited continuing professional development training in e-mental health primary care is available through federally funded initiatives, such as e-Mental Health in General Practice (eMHPrac; available online at www.blackdoginstitute.org.au/eMHPrac).

Step 2: moderate depression

Although patients with moderate depression may also benefit from evidence-based e-interventions, face-to-face psychological therapies are indicated, such as interpersonal psychotherapy (IPT) or cognitive behaviour therapy (CBT). For patients who do not want, cannot access or do not benefit from such psychological therapies, antidepressants should also be considered.

Step 3: severe depression

Patients with depression resistant to the above treatments or who present initially with severe or melancholic depression are best managed with the advice of or in conjunction with a psychiatrist. They will often require antidepressant medication and combined treatments, including more complex psychotherapeutic approaches. Local public mental health after-hours or crisis services may also need to be part of the patient's care team.

Step 4: severe depression with marked functional impairment

Patients with depression that is accompanied by psychotic symptoms, severely impairs their functioning, has failed to respond to multiple adequate courses of antidepressants or is life-threatening may require treatment in hospital. This treatment may include electroconvulsive therapy (ECT).

Relapse prevention

Both structured psychotherapy (such as CBT) and antidepressants are efficacious in the prevention of relapse or recurrent episodes of depression. For a first episode of moderate depression, we recommend continuing antidepressants for six months after symptom remission. However, in patients with a clear pattern of multiple episodes of moderate or severe depression over time, antidepressants should be continued for several years, and even lifelong in those with a history of frequent and difficult-to-treat recurrences of illness.

Initiating pharmacotherapy

Consider pharmacotherapy for patients with moderate or severe depression, those presenting with mild depression that does not respond to nonpharmacological interventions and those with a past history of moderate or severe depression.

Before beginning antidepressants, reassess the patient's mental state (including suicidality), the diagnosis and especially the possibility of untreated comorbid disorders. For example, anxiety disorders and substance abuse are commonly comorbid with depression and require their own evidence-based interventions if the patient's depression is to respond fully to treatment.

Depression is a risk factor for treatment nonadherence, so it is vital to establish a therapeutic alliance and to educate patients and families about treatment adherence. Develop a plan to monitor the patient's treatment response, side effects and general medical condition.

Remission is the initial goal. Although patients should be reviewed every two weeks when initiating antidepressants, the overall response should be assessed at four weeks, and strategies optimised if the response is inadequate. Up to 10 weeks may be required to achieve maximum improvement.

Choosing an initial antidepressant

When choosing an antidepressant, consider patient factors as well as characteristics of the drugs. Important patient factors include:

- prior experience with antidepressants
- history of adherence to treatment
- preference, especially with regard to potential side effects such as sexual dysfunction
- concurrent medical conditions (such as cardiac disorders)
- use of nonpsychiatric drugs
- suicidality.

Also important is one's own prescribing experience with antidepressants.

Efficacy and tolerability

In the treatment of mild to moderate depression, no one class of antidepressant is quicker in onset or more effective than other classes. Escitalopram, sertraline, venlafaxine and mirtazapine have some relative benefits when considering the severity of the depressive episode and dosage required. Reboxetine has a lower response rate than other antidepressants.[10]

Given the similarities in efficacy of most antidepressants, the most important factors to consider in the first choice of antidepressant are often tolerability and safety (although some patients uniquely respond to some medicines and not others). Overall, selective serotonin

3. SIDE EFFECTS OF COMMON ANTIDEPRESSANT GROUPS

Selective serotonin reuptake inhibitors (SSRIs)

- The most frequent side effects are nausea or gastrointestinal pain, activation/restlessness, sexual dysfunction and headaches
- Bleeding risk is increased as SSRIs alter platelet function, especially in combination with other substances influencing platelet dysfunction
- There is a risk of hyponatraemia due to syndrome of inappropriate antidiuretic hormone secretion (SIADH), especially in the elderly
- QTc prolongation has been associated with high doses of SSRIs (e.g. greater than 40 mg of citalopram)

Tricyclic antidepressants (TCAs)

- Anticholinergic, antimuscarinic and cardiovascular side effects mean that TCAs are relatively contraindicated in patients with cardiovascular disease
- TCAs are also contraindicated in patients with narrow angle glaucoma, prostatic hypertrophy, cognitive impairment, seizure or delirium
- Secondary amine TCAs (e.g. nortriptyline) have fewer side effects than tertiary amine TCAs (e.g. amitriptyline)

Serotonin and noradrenaline reuptake inhibitors (SNRIs)

- Side effects include nausea, dizziness, somnolence, insomnia, ejaculatory abnormalities, sweating and dry mouth Increased bleeding risk is associated with platelet dysfunction

Mirtazapine

- Rates of cessation due to side effects of weight gain and sedation are similar to those with SSRIs
- Nausea and sexual side effects are less common than with SSRIs

Vortioxetine

- Side effects are similar to those of other SSRIs, with nausea the most common
- Maximum recommended dose is 10 mg/d in patients known to be cytochrome P450 2D6 poor metabolisers[12]
- May have a positive cognitive effect although this requires further research to verify[13]

Agomelatine

- Poses an increased risk of liver damage with up to a 10-fold increase in serum transaminase levels and some reported cases of liver failure, hepatitis and icterus

Sexual dysfunction

- TCAs, SSRIs and venlafaxine are more likely to cause sexual dysfunction than duloxetine, reboxetine and mirtazapine. Agomelatine and perhaps vortioxetine are the least likely to cause sexual dysfunction

reuptake inhibitors (SSRIs) are generally better tolerated than older style antidepressants such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs).

Significant symptoms

Significant symptoms such as anxiety and insomnia may also influence the initial choice of antidepressant. Escitalopram and other SSRIs or the serotonin and nonadrenaline reuptake inhibitor (SNRI) venlafaxine can be useful first choices for patients with anxious rumination as a prominent associated symptom. The melatonergic antidepressant agomelatine or the tetracyclic antidepressant mirtazapine may be preferred when disturbances of the sleep–wake cycle or insomnia are prominent. There is evidence that the SNRI duloxetine is helpful in patients with comorbid physical pain.[10]

Depressive subtype

Atypical depression. Major depression with atypical features describes depression with key features that are the opposite of those in the usual presentation of depression (Box 2).

SSRIs can be helpful in the treatment of patients with atypical depression, and evidence-based psychological therapies (e.g. CBT, IPT) often have a key role in these patients. Classically, older MAOIs have been reported to be effective in patients with atypical depression; in contemporary practice, these are preferably initially prescribed by psychiatrists.

Major depressive disorder with melancholic features. This type of depression is almost always severe. Key features are:

- marked anhedonia (loss of pleasure in almost all activities and/or a lack of reactivity to usually pleasurable stimuli)[6]
- together with three or more of the following features:
  - despondency, despair, moroseness or 'empty mood'
  - these symptoms worse in the morning
  - early morning wakening
  - marked psychomotor retardation or agitation
  - significant anorexia or weight loss
  - excessive or inappropriate guilt.

Patients with major depressive disorder with melancholic features are nearly always managed by GPs with advice from or in conjunction with a psychiatrist. Antidepressants of choice include the well-tolerated SSRIs, SNRIs such as venlafaxine, TCAs, MAOIs and the newer antidepressants such as agomelatine and the serotonin inhibitor and modulator vortioxetine.

Psychotic depression. Major depressive disorder associated with delusions and/or hallucinations is always severe and has a considerably better response rate when treated with the combination of an antidepressant and an antipsychotic than with either alone.[11] This benefit must be weighed against potential unwanted effects, such as extrapyramidal symptoms and the metabolic syndrome. Some patients will also respond better to ECT (see below.)

Side effect profiles

The side effect profiles of the different classes of antidepressant are summarised in Box 3.[12,13] In general, SSRIs have greater tolerability than other antidepressants.

4. ANTIDEPRESSANTS AND SUICIDALITY

- Epidemiological studies reveal an association between a reduction in the frequency of suicides and an increase in the number of prescriptions for antidepressants in the past two to three decades.[17]
- It has been shown that the risk of suicide is highest in the month before starting an antidepressant, rapidly declines in the first week of treatment, and continues to decrease to even lower stable rates as treatment continues.[18]
- A meta-analysis of trial data submitted to the US Food and Drug Administration (FDA) confirmed previous findings that suicidal behaviour did not differ between those taking antidepressants and those taking placebo.[19]
- An increase in suicidality (but not completed suicides) among adolescents led to the FDA's black box warning on antidepressant medication for youths in 2004, but several subsequent studies have shown an inverse relation between antidepressant prescribing and successful suicide in this age group.[20-22]

Drug–drug interactions

Some newer antidepressants (venlafaxine, mirtazapine, duloxetine, agomelatine and reboxetine), although also metabolised through hepatic CYP450 systems, are associated with lower rates of drug–drug interactions than SSRIs.[14]

Serotonin syndrome has been most commonly due to the interaction of an MAOI and an SSRI but can occur with other combinations of serotonergic medications (e.g. clomipramine, L-tryptophan, buspirone, venlafaxine, tramadol, St John's wort, unregulated performance enhancing 'supplements' and, in rare cases, lithium). Serotonin syndrome can present with confusion, agitation, myoclonus, hyperreflexia, sweating, shivering, tremor, abdominal cramps, diarrhoea, tachycardia and hypotension or hypertension.[15] It may rarely result in death. Although serotonin syndrome can occur idiosyncratically, it is more likely with higher doses.

A handy guide to switching patients between antidepressant classes, especially to avoid serotonin syndrome, is available on the Black Dog Institute's website (http://www.blackdoginstitute.org.au/healthprofessionals/depression/using antidepressants/index.cfm).[16]

Suicidality

Although effective antidepressants reduce the intensity of suicidal thoughts over time, there is no specific acute antisuicidal medication. Lithium taken prophylactically prevents both suicide attempts and completed suicide but any acute antisuicidal effects are not known.[1] Evidence on the relation between antidepressants and suicidality is discussed in Box 4.[17-22]

Suicidal or young patients commencing an antidepressant should be seen at least weekly and frequently thereafter until the risk of suicide is no longer considered clinically important.[23]

Overdose danger

TCAs are the most dangerous of the antidepressants in overdose, followed by SNRIs (and others such as mirtazapine), with SSRIs being least dangerous.[24] If patients with suicidality require one of the antidepressants that are more dangerous in overdose then we recommend that only a week's supply be prescribed (or dispensed) at a time.

Evaluating effectiveness of initial treatment

Observer ratings (e.g. the Hamilton Rating Scale for Depression), patient report (e.g. Beck Depression Inventory and the PHQ-9) as well as patient monitoring of mood may all be helpful in determining response to initial treatment.

Difficult-to-treat depression

Only a third of patients with depression initially treated with an SSRI achieve remission.[25] The STAR*D (Sequenced Treatment Alternatives to Relieve Depression) trial of almost 3000 patients with depression in the USA took an algorithmic approach to difficult-to-treat depression and found that 70% of patients eventually achieved remission, but only after trying up to four different antidepressant treatment approaches.[25] This highlights the importance of using the best available evidence in the management of difficult-to-treat depression.[26]

Before adopting a pharmacological strategy for a patient with difficult-to-treat depression, consider:

- general clinical issues, such as incorrect or missed comorbid psychiatric diagnoses (e.g. bipolar disorder, schizophrenia, anxiety disorders) as well as substance abuse, persisting psychosocial issues and treatment nonadherence
- the adequacy of the antidepressant dose; consider measuring plasma levels of the antidepressant (to identify fast or slow metabolisers or nonadherence despite claimed adherence) and the possibility of drug interactions with nonpsychiatric medications
- a review of physical health, including assessing for poorly controlled pain or a general medical condition that is contributing to the depression (Box 5).

Although there is no strong evidence supporting the particular order of implementing evidence-based pharmacological strategies in patients with difficult-to-treat depression, the following sequence is recommended (see Box 6):[26]

1. increase antidepressant dose
2. switch to different antidepressant
3. augment with a nonantidepressant agent
4. combine antidepressants.

Sometimes it may be more appropriate to consider augmentation before switching antidepressants. Psychological interventions or neurostimulatory treatments such as ECT (see below) should be considered at each step in management.[26]

5. MEDICAL CONDITIONS THAT CONTRIBUTE TO DEPRESSION

- Degenerative neurological disorders
- Cardiovascular diseases
- Epilepsy
- Brain tumour
- Endocrine disorders (especially thyroid dysfunction, hyper- and hypoadrenocorticism, hyper- and hypoparathyroidism, diabetes mellitus)
- Metabolic conditions such as vitamin B_{12} and folate deficiency
- Systemic autoimmune diseases such as systemic lupus erythematosus
- Viral and other infections
- Some cancers (e.g. pancreatic and lung cancer)

Maximising the dose of the initial antidepressant

Increasing the antidepressant dose to the recommended maximum can be helpful for TCAs that have a broad therapeutic range (e.g. amitriptyline, clomipramine), tetracyclic antidepressants (e.g. mirtazapine), venlafaxine and the MAOI tranylcypromine.[10,27] Increased doses of SSRIs, however, are generally not more efficacious as there is usually 80% receptor occupancy with the minimum recommended dose, although some studies do suggest a benefit of higher SSRI doses.[28] If a maximum tolerable approved dose has been administered for four weeks and there is still no response then switching medications is reasonable. If there is a partial response then the same dose could be continued for a further four weeks.

Switching to a different antidepressant

The current evidence indicates that after failure to respond to an initial SSRI, acceptable next options include a different SSRI or an antidepressant of a different class (such as an SNRI).

Augmenting with a non-antidepressant

Adding use of a nonantidepressant to an antidepressant to which there has been only a partial response can be helpful. Some options include:

- lithium, which is more effective than placebo in augmentation of TCAs, SSRIs and other antidepressants.[29] A once-daily dose to achieve plasma levels of 0.5 to 1.0 mmol/L is recommended
- atypical antipsychotics. Despite strong evidence from placebo-controlled trials that augmenting antidepressants with antipsychotics is more effective than augmenting with placebo, any such benefits must be weighed against unwanted effects such as weight gain, sedation, prolactin increase and extrapyramidal side effects. Moreover, such use of antipsychotics has not been approved by the TGA in Australia, and would therefore be considered 'off-label' prescribing in this country.

Among the atypical antipsychotics, evidence supporting effectiveness is more ambiguous for olanzapine. In the case of risperidone, initial improvement was not maintained through continuation phase treatment.[1] For aripiprazole, the recommended starting dose is 2 to 5 mg per day, with dose adjustments of 5 mg daily at intervals of no less than one week, with a maximum dose of 15 mg daily. Quetiapine extended release should be started at a dose of 50 mg at night, which can be increased on day 3 to 150 mg at night. Doses higher than 300 mg daily have not been studied as an augmentation strategy.

Combining antidepressants

It has been argued that the combined effects of two antidepressants with different mechanisms of action can improve the response in patients with difficult-to-treat depression. For example, a recent meta-analysis found that both TCAs and mirtazapine in combination with SSRIs were more effective than an SSRI alone in achieving remission, with no difference in rates of drop out or side effects in those studies that reported on these data.[30] Nevertheless, not all research has supported this strategy, nor are all combinations safe.[10] Prescribers must be aware, for example, of the danger of serotonin syndrome (see above) when combining two antidepressants.

6. PHARMACOLOGICAL TREATMENT RECOMMENDATIONS FOR DIFFICULT-TO-TREAT DEPRESSION[26]

1. Increase antidepressant dose
- The maximum tolerable approved dose should be prescribed for at least four to six weeks

2. If no or partial response, consider switching to another antidepressant
- Different SSRI
- Non-SSRI antidepressant (e.g. venlafaxine or other SNRI, mirtazapine, TCA, MAOI or bupropion*)

3. If no or partial response, consider augmenting with a nonantidepressant agent
- Lithium
- Atypical antipsychotic

4. If nil or partial response, consider combining antidepressants
- SSRI plus mirtazapine
- Mirtazapine plus venlafaxine (or other SNRI)
- SSRI plus TCA
- SSRI plus bupropion*

Abbreviations:
MAOI = monoamine oxidase inhibitor;
SNRI = serotonin and noradrenaline reuptake inhibitor;
SSRI = selective serotonin reuptake inhibitor;
TCA = tricyclic antidepressant.

* Bupropion is not approved for the indication of depression in Australia.

Physical treatments for difficult-to-treat depression

In Australia, current approved neurostimulation treatments for patients with depression are ECT and repetitive transcranial magnetic stimulation (rTMS). Transcranial direct current stimulation is in development, with research suggesting it may emerge as a promising treatment for depression in the near future.

Electroconvulsive therapy

ECT is the most effective proven biological treatment that is currently available for depression. It is prescribed for severe or treatment-resistant unipolar and bipolar depression, especially in patients with psychotic symptoms,

refusal to eat or high suicide risk.[31]

Newer forms of ECT, such as the use of ultrabrief pulses ('ultrabrief ECT') and bifrontal ECT, have been shown to have lesser cognitive side effects than standard ECT while still achieving high efficacy.[32] ECT is a safe procedure, with high levels of patient acceptability and satisfaction.[33-36] Clinical data and studies in animal models have repeatedly demonstrated that ECT does not produce brain damage.[37,38]

Repetitive transcranial magnetic stimulation

Repetitive TMS generates a strong magnetic field through a coil placed on the scalp. Magnetic fields cross the skull unimpeded and induce electrical currents, depolarising neurons in the cortex. Sessions of rTMS treatment take approximately 30 to 40 minutes and are typically given every weekday over three to six weeks. The treatment is nonconvulsive, does not require anaesthesia and is safe and well tolerated, with no cognitive impairment.[39] It is, however, clearly less efficacious than ECT in the treatment of patients with depression, especially depression with psychotic features.[40-43]

Although rTMS machines have been approved by the TGA to treat depression in adults who have failed to respond adequately to antidepressant medication, rTMS is not, at this time, subsidised by the MBS. In Australia, it is accessible to those with private health insurance in some private inpatient and day-patient settings and on a fee-for-service basis in some outpatient treatment centres.

Repetitive TMS is suitable for depressed patients who have not responded to antidepressant medication, cannot tolerate side effects of medication or prefer a nonmedication option. However, patients need to be screened for their suitability for receiving magnetic stimulation, which includes assessing for neuropathology, (which may increase the risk of seizure) and metal implants or fragments in the head.

Conclusion

Depression is a common presentation in general practice. Much distress in patients and families can be alleviated when it is well managed. A stepped approach to mental health care can ensure timely access to evidence-based treatment for all those experiencing depression. The described approach also highlights the advantages of e-mental health interventions as well as newer pharmacotherapy and neurostimulation treatments. MT

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A list of references is included in the website version (www.medicinetoday.com.au) and the iPad app version of this article.

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JOSEPHINE ANDERSON BA, BMed(Hons), MMed, MHealthLaw, FRANZCP, Cert Child Adol Psych; **VERONICA GALVEZ** MB BS, MD; **COLLEEN LOO** MB BS(Hons), FRANZCP, MD; **PHILIP B. MITCHELL** AM, FASSA, MB BS, MD, FRANZCP, FRCPsych

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