

# Treating depression: the *beyondblue* guidelines for treating depression in primary care

“Not so much what you do but that you keep doing it”

Pete M Ellis and Don A R Smith

DEPRESSION IS A COMMON MENTAL DISORDER in the Australian community.<sup>1,2</sup> The recent national survey of Mental Health and Wellbeing indicated that approximately 18% of people suffered a psychiatric disorder in the 12 months prior to the survey, of whom 38% presented to a healthcare service; of these, 76% presented to a general practitioner.<sup>1</sup> Most people with depression experience significant disruption to their normal lifestyle.<sup>2</sup> In addition, many have comorbid anxiety or substance-misuse disorders.<sup>1</sup> Because of the high prevalence of depression, its consequent disability and the central role of the GP, it is particularly important that quality care be provided for depression in the primary care sector.

To date, most guidelines for the treatment of depression have focused on severe depression in secondary care settings.<sup>3,4</sup> However, the patterns of illness and comorbidity with anxiety, substance misuse and medical illness in these settings differ substantially from those found in general practice. Therefore, *beyondblue: the national depression initiative*<sup>5</sup> commissioned these guidelines in recognition of the pivotal role of the primary care sector in the delivery of treatment and management of depression, and the current lack of evidence-based guidelines to guide healthcare professionals and assist consumers in these settings. These guidelines are based on the standard process for guideline development.<sup>6</sup>

## Review of the evidence

A literature search for randomised controlled trials of treatments for depression was conducted using three strategies: a search of the MEDLINE and PsychLit databases for studies published between 1996 and 2001; an examination of earlier studies reported in the literature obtained from the MEDLINE and PsychLit database searches; and a manual search through medical journals with an impact factor greater than 0.86 dating from 1996 to December 2001. The database search was conducted using the terms “depression” (or “major depression” or “major depressive disorder”) and “RCT” (or “meta-analysis” or “review”). Studies

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## ABSTRACT

- Most people with depression will be treated in general practice, either by the GP alone, or (for more serious depression) in partnership with specialist mental health services.
- Treatment plans should always be based on thorough assessment, including the type, severity and duration of the depressive episode, and any stressors that contributed to the episode.
- For mild and moderate depression, meta-analysis shows there is little difference in relative effectiveness of treatments, and continuation of therapy is more important than initial treatment choice.
- The best outcomes are likely when a good therapeutic alliance is formed between a healthcare professional and the patient, and adequate treatment is provided over a long enough period. For pharmacological interventions, treatment should continue for:
  - at least one year for a first episode of depression, and
  - at least two years for repeated episodes or where there are other risk factors for relapse.

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prior to 1996 were taken from the meta-analysis reported by the Agency for Health Care Policy and Research,<sup>7</sup> and from reference lists of published meta-analyses.

Studies were considered to be of mild depression if the inclusion criterion for the study was a minimum score of 12, and of moderate depression if the minimum score was 17, on the Hamilton Rating Scale for Depression (Box 1).<sup>8</sup> Studies of patients with severe depression (minimum score of 24 on the Hamilton Rating Scale) were not included.

For each study, “numbers needed to treat” (NNT) and “absolute risk reduction” (ARR) were calculated (Box 2), and a meta-analysis was completed. Recommendations were then developed (see ‘Background and evidence-base’ box for details).

## Results

From the literature search, 1062 articles were retrieved, of which 382 were randomised controlled trials. Of these, 107 met the inclusion criteria and had data on response rates required for calculating the NNT.

### 1: Hamilton Rating Scale for Depression<sup>8</sup>

The Hamilton Rating Scale is designed to be used only on patients already diagnosed as suffering from depression. It is used for quantifying the results of an interview, and its value depends on the skill of the interviewer in eliciting the information.

The scale contains 21 items: depressed mood, feelings of guilt, suicide, insomnia early, insomnia middle, insomnia late, work and activities, retardation (psychomotor), agitation, anxiety (psychological), anxiety (somatic), somatic symptoms (gastrointestinal), somatic symptoms (general), genital symptoms, hypochondriasis, loss of weight, insight, diurnal variation, depersonalisation and derealisation, paranoid symptoms, and obsessional and compulsive symptoms.

Each item is measured on a five-point or three-point (for items that are more difficult to quantify) scale, and the scores are summed. The higher the score, the more severe the depression.

A score of 12 or higher indicates mild depression, 17 or higher indicates moderate depression, and 24 or higher indicates severe depression.

### 2: Definitions

The *number needed to treat* (NNT) is a common measure in analyses of effectiveness, and indicates the number of people who would have to receive the given treatment to have one additional person relieved of symptoms of depression by the selected treatment compared with the comparison treatment. A lower NNT indicates a relatively more effective treatment.

The *absolute risk reduction* (ARR) is the percentage difference in treatment response rate between the selected treatment and the comparator (ie, placebo or another treatment). The more "relatively effective" the treatment, the greater the ARR.

For both NNT and ARR, "response" refers to at least 50% reduction in initial severity of symptoms as measured by the Hamilton Rating Scale for Depression<sup>8</sup> (Box 1) (or similar instrument) and calculated on the basis of an intention-to-treat criteria analysis.

Where there were few studies on a particular compound, or a small number of subjects, the confidence limits around the estimates were very large. In such cases, the resulting NNT and ARR need to be treated with caution, as the estimate of the relative effectiveness of the treatment is imprecise.

Box 3 summarises the results of the meta-analysis. For both mild and moderate depression there was little difference between the relative effectiveness of treatments as indicated by both the NNT and ARR values. The exceptions were that, for moderate depression, tricyclic antidepressants (TCAs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) were significantly more effective than placebo (95% confidence intervals did not overlap those for placebo treatments). No other treatment comparisons were statistically significant, either because of the variance in the studies (especially when there were a large number of studies and large sample sizes) or because of the small number of studies (and small sample sizes).

There were few studies of treatments for mild depression, but, in those reported, problem-solving led to the best outcome. Problem-solving was as effective as a TCA and probably more effective than a selective serotonin reuptake inhibitor (SSRI).

For moderate depression, treatment with antidepressants (eg, TCA, SSRI and other antidepressants, including mirta-

zapine, nefazodone and reboxetine) had similar effectiveness compared with placebo or other active treatments. In the studies comparing two antidepressant treatments, venlafaxine had the greatest relative benefit, but an additional 10 people with depression would have had to be treated with this drug rather than another antidepressant for one more person to respond. Thus, the difference was statistically significant but of marginal clinical importance in this population.

Our analysis suggests that there is less to be gained from the selection of a particular treatment than from good compliance with any of these treatments.

Other key factors in selecting an antidepressant treatment include the side-effect profiles, patient preferences (and thus likely increased compliance), and the nature of the symptoms (which may be differentially addressed by different treatments). Other individual factors may be particularly germane to selection of a psychological approach.

Although it is possible to calculate side-effect rates for given compounds based on clinical trials, these are influenced by the means of ascertaining them. For example, the initial reported rate of sexual dysfunction with fluoxetine, based on volunteered complaints, was 2.7%, but later studies reported rates as high as 75%.<sup>115</sup> This is not a unique situation, and specific enquiries are essential to ascertain an individual's own experience of side effects.

### Recommendations

Although the treatment of severe depression should involve a partnership between the patient, the GP and a secondary mental health service, most people have mild to moderate depression and will usually be treated by a GP. Even for the minority of people experiencing severe and complicated depression, referral to specialist mental health services for assessment or specialised non-pharmacological treatment generally occurs only during the acute treatment phase.<sup>3</sup> The GP still provides or coordinates most of the treatment for most of these people.

Thorough assessment is essential to the development of appropriate individual treatment plans. Assessment should include the determination of type, severity and duration of the depressive episode. It is also important to discover the stressors that have contributed to or exacerbated the episode, and to examine the supports and resources the person has to assist with coping. It is also essential to assess the risk of suicide (or self-harm) and risk to others, either through violence or through neglect (eg, care of babies or young children during the postpartum period).

Treatment decisions will vary based on the type of depression, current severity, duration and history. Repeated formal assessment of severity (eg, using the Hamilton Rating Scale for Depression, Center for Epidemiological Studies Depression Scale,<sup>116</sup> or other, similar scales) will assist with the selection of evidence-based treatment(s) and facilitates monitoring of the effectiveness of treatment.

The best outcomes are likely when a good therapeutic alliance is forged between a healthcare professional and the

**3: Overview of the meta-analysis used in the formulation of the advice in the *beyondblue* guidelines**

	Number of studies	Number of patients	Number needed to treat	Absolute risk reduction
<b>Comparisons versus placebo</b>				
Mild depression*				
SSRIs <sup>9,10</sup>	2	103	10.2	9.8%
Problem-solving <sup>11</sup>	1	60	3.0	33.0%
Moderate depression*				
All TCAs <sup>†12-28</sup>	17	3000	4.7	21.2%
All SSRIs <sup>10,13-21,29-40</sup>	22	3442	5.5	18.2%
SNRIs (eg, venlafaxine) <sup>†28,41-43</sup>	4	1050	4.8	21.0%
NARIs (eg, reboxetine) <sup>36</sup>	1	254	4.7	21.1%
NaSSAs (eg, mirtazapine) <sup>12,44,45</sup>	3	298	4.1	24.2%
Serotonin (5-HT <sub>2</sub> ) antagonists (eg, nefazodone) <sup>22,24,26,46</sup>	4	572	5.4	18.5%
Cognitive behaviour therapy <sup>23,47-49</sup>	4	347	5.4	18.7%
<b>Comparisons versus active treatment</b>				
Mild depression				
SSRIs vs TCAs <sup>50-53</sup>	4	352	10.4	9.7%
RIMAs (eg, moclobemide) vs other antidepressants <sup>54-56</sup>	3	189	11.1	9.1%
Problem-solving vs TCAs <sup>11,57</sup>	2	177	129.0	0.8%
Counselling vs antidepressants <sup>58</sup>	1	103	7.7	13.0%
Moderate depression				
All TCAs vs SSRIs <sup>13,15-21,40,50,52,59-97</sup>	50	7600	96.3	1.0%
Venlafaxine vs other antidepressants <sup>28,43,98-103</sup>	8	1925	10.9	9.2%
Reboxetine vs other antidepressants <sup>36,62</sup>	2	707	15.5	5.7%
Mirtazapine vs TCAs <sup>12,44,45,104,105</sup>	5	722	40.1	2.5%
Nefazodone vs SSRIs <sup>22,24,26,106</sup>	4	570	25.3	4.0%
RIMAs (eg, moclobemide) vs SSRIs <sup>107-110</sup>	4	340	22.0	4.5%
Cognitive behaviour therapy vs antidepressants <sup>23,49,111-114</sup>	6	833	43.8	2.3%

\* No valid trials for moclobemide versus placebo were found. † The 95% confidence intervals of both number needed to treat and absolute risk reduction indicate that TCAs and SNRIs are more effective than placebo. Other comparisons did not reach this level of significance. SSRI = selective serotonin reuptake inhibitor. TCA = tricyclic antidepressant. SNRI = serotonin and noradrenaline reuptake inhibitor. NARI = noradrenaline reuptake inhibitor. NaSSA = noradrenaline-serotonin specific antidepressant. RIMA = reversible inhibitor of monoamine oxidase A.

patient, and adequate treatment is provided over a long enough period.

For the initial treatment (first-line), our meta-analysis shows there is little difference between the major pharmacological and psychological treatment options for mild to moderate depression. When a sufficient response to the initial treatment is not attained, second- and third-line treatments are indicated (Box 4). All pharmacological (and, to a lesser extent, psychological) treatments have a high relapse rate among people who discontinue treatment early.<sup>117</sup>

Although there is increasing evidence that cognitive behaviour therapy (CBT) and interpersonal therapy (IPT) are as effective as antidepressants in many depressive illnesses, not all therapists are equally experienced or effective in delivering these interventions.<sup>118,119</sup> CBT and IPT should only be considered if a competent and experienced practitioner is available. There are too few studies of other forms of psychological therapies to recommend that any are of

similar benefit to CBT and IPT, although clinical experience suggests they can be valuable for those with major interpersonal difficulties and severe past trauma.

**Evidence-based treatment recommendations**

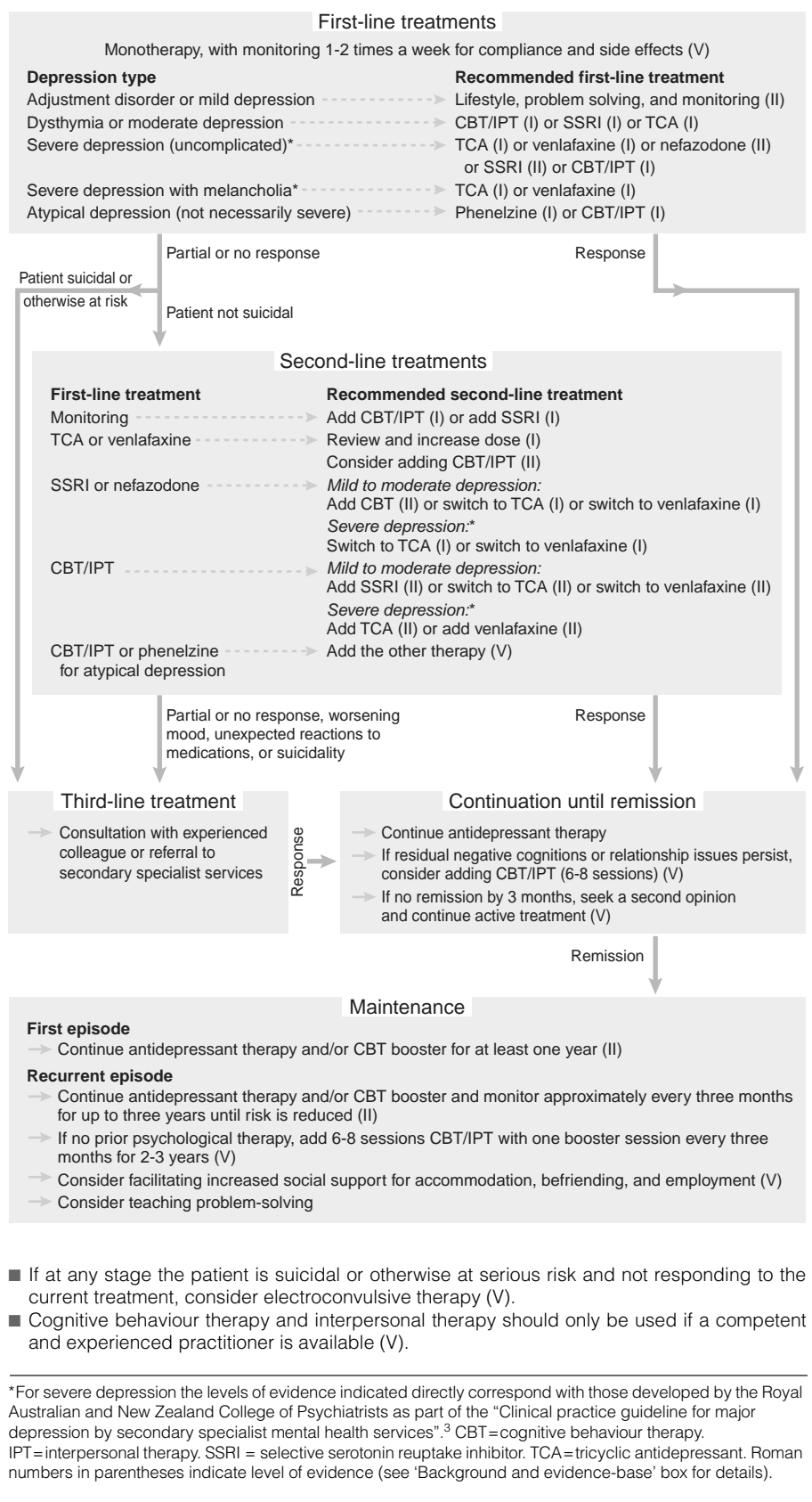
The evidence supports the following treatment recommendations as part of an overall clinical management plan.

**Initial treatment**

**All patients:** Provide education about depression and lifestyle changes that will assist recovery (be mindful of identified stressors and supports). This should be ongoing to maintain any changes achieved, and repeated if life circumstances change. A check should be made for any risk of suicidal thoughts (level of evidence = V).

**Mild depression without complications:** Reinforce education and lifestyle changes. Consider teaching problem-solving techniques and conducting an assessment of the

#### 4: Flowchart summary of recommendations for treating depression in general practice



quality of relationships with significant others. Offer specific assistance as required and provide supportive monitoring.

Unless the symptoms persist beyond eight weeks, there is no evidence for the use of pharmacological or psychological treatments for these patients. If symptoms persist, brief treatment with CBT, IPT or an SSRI, in addition to supportive management, may assist (level of evidence [overall] = I; level of evidence [use of problem solving] = II).

#### **Moderate depression (including with comorbid anxiety) and dysthymia:**

Treat with an antidepressant or one of the brief psychological therapies (eight to 12 sessions of CBT or IPT<sup>120,121</sup>). Monitor for side effects (at least twice a week by telephone), and encourage compliance with the selected treatment. If after six to eight weeks symptoms still persist (partial or no response), consider changing to a second- or third-line treatment option (level of evidence [use of antidepressant or CBT] = I; level of evidence [monitoring] = V).

**Moderate depression with comorbid substance misuse:** Use interventions to reduce alcohol consumption and implement treatments as outlined for moderate or severe depression (level of evidence = V).

**Severe depression with melancholia:** Obtain an opinion from a colleague with appropriate experience or specialist mental health service. In general, initiate an antidepressant and, when there has been a response, consider adding psychological therapy (to achieve a full response or reduce risk of relapse<sup>122-127</sup>) (level of evidence = I).

**Recurrent depression or failure to respond to a preferred first-line treatment:** If the first-line treatment was an SSRI or psychological therapy, switch to a TCA or venlafaxine, or combine a course of one of the brief psychological therapies with an antidepressant<sup>111,118,128</sup> (level of evidence [switching to TCA or venlafaxine] = I; level of evidence [use of antidepressant with CBT] = II). (For other options, see Box 4.)

**Psychotic depression, severe depression with risk of suicide, and atypical depression:** Refer to specialist mental health services (level of evidence = V).

### Background and evidence base

Articles retrieved through a literature search were reviewed by a working group, which developed recommendations for the management of depression in primary care. These recommendations were discussed extensively by a panel of 11 general practitioners convened by *beyondblue*, which led to some modification of the original recommendations.

#### Working group

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#### Levels of evidence used in these guidelines

- I Evidence obtained from a systematic review of all relevant randomised controlled trials
- II Evidence obtained from at least one well designed randomised controlled trial
- III Evidence obtained from at least one non-randomised controlled trial
- IV Evidence obtained from at least one case-series or test-retest study
- V Peer-reviewed expert opinion

### Continuing treatment

The most important factor is to maintain compliance with an effective treatment. Addition of CBT or IPT to the continuation and maintenance phases is associated with lower relapse rates (level of evidence = I).

### Maintenance treatment for recurrent depression

As depression is often a relapsing condition, ongoing prevention of relapse and early intervention in any recurrence is essential. Indeed, most presentations, even to primary care providers, are for a second or subsequent episode of depression, and the treatments offered should acknowledge this. In this respect depression is similar to many medical conditions, such as congestive heart failure or basal cell carcinoma. Once a person has presented with one of these conditions, the likelihood of developing a second episode is considerably greater. Prevention and monitoring for early indications of relapse therefore needs to be ongoing.

The key intervention should be continuing with an effective and acceptable treatment.<sup>129</sup> The use of CBT or IPT when there are residual symptoms, or when an adequate response has not been achieved, has been associated with lower rates of relapse after two and three years<sup>128,130</sup> (level of evidence [continuing with an effective treatment] = I; level of evidence [CBT/IPT for residual symptoms] = II).

### Conclusion

As there is little difference in the relative effectiveness of treatments for mild to moderate depression, continuation of therapy to full remission and to prevent relapse is more important than initial treatment choice. The best outcomes are likely when a good therapeutic alliance is forged between a healthcare professional and the patient, and an adequate treatment is provided over a long enough period. For a first episode of depression and for pharmacological treatments, this would be for at least one year, but for repeated episodes or where there are other risk factors for relapse this should be for at least two years. That is, *it is not so much what you do but that you keep doing it.*

### Competing interests

P M Ellis receives research funds from Eli Lilly for a study of antipsychotic drugs. He has a managed share portfolio that contains some pharmaceutical company shares.

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