

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.^{1,2} 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.¹ Most people with depression experience significant disruption to their normal lifestyle.² In addition, many have comorbid anxiety or substance-misuse disorders.¹ 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.^{3,4} 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*⁵ 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.⁶

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

Department of Psychological Medicine, Wellington School of Medicine and Health Sciences, University of Otago, Wellington South, New Zealand.

Pete M Ellis, PhD, FRANZCP, Professor of Psychological Medicine;
Don A R Smith, MA(Hons), Research Associate.

Correspondence: Professor Pete M Ellis, Department of Psychological Medicine, Wellington School of Medicine and Health Sciences, University of Otago, PO Box 7343, Wellington South, New Zealand.
ellis@wnmeds.ac.nz

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.

MJA 2002; 176: S77–S83

prior to 1996 were taken from the meta-analysis reported by the Agency for Health Care Policy and Research,⁷ 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).⁸ 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 Depression⁸

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 Depression⁸ (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%.¹¹⁵ 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.³ 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,¹¹⁶ 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
Comparisons versus placebo				
Mild depression*				
SSRIs ^{9,10}	2	103	10.2	9.8%
Problem-solving ¹¹	1	60	3.0	33.0%
Moderate depression*				
All TCAs ^{†12-28}	17	3000	4.7	21.2%
All SSRIs ^{10,13-21,29-40}	22	3442	5.5	18.2%
SNRIs (eg, venlafaxine) ^{†28,41-43}	4	1050	4.8	21.0%
NARIs (eg, reboxetine) ³⁶	1	254	4.7	21.1%
NaSSAs (eg, mirtazapine) ^{12,44,45}	3	298	4.1	24.2%
Serotonin (5-HT ₂) antagonists (eg, nefazodone) ^{22,24,26,46}	4	572	5.4	18.5%
Cognitive behaviour therapy ^{23,47-49}	4	347	5.4	18.7%
Comparisons versus active treatment				
Mild depression				
SSRIs vs TCAs ⁵⁰⁻⁵³	4	352	10.4	9.7%
RIMAs (eg, moclobemide) vs other antidepressants ⁵⁴⁻⁵⁶	3	189	11.1	9.1%
Problem-solving vs TCAs ^{11,57}	2	177	129.0	0.8%
Counselling vs antidepressants ⁵⁸	1	103	7.7	13.0%
Moderate depression				
All TCAs vs SSRIs ^{13,15-21,40,50,52,59-97}	50	7600	96.3	1.0%
Venlafaxine vs other antidepressants ^{28,43,98-103}	8	1925	10.9	9.2%
Reboxetine vs other antidepressants ^{36,62}	2	707	15.5	5.7%
Mirtazapine vs TCAs ^{12,44,45,104,105}	5	722	40.1	2.5%
Nefazodone vs SSRIs ^{22,24,26,106}	4	570	25.3	4.0%
RIMAs (eg, moclobemide) vs SSRIs ¹⁰⁷⁻¹¹⁰	4	340	22.0	4.5%
Cognitive behaviour therapy vs antidepressants ^{23,49,111-114}	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.¹¹⁷

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.^{118,119} 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

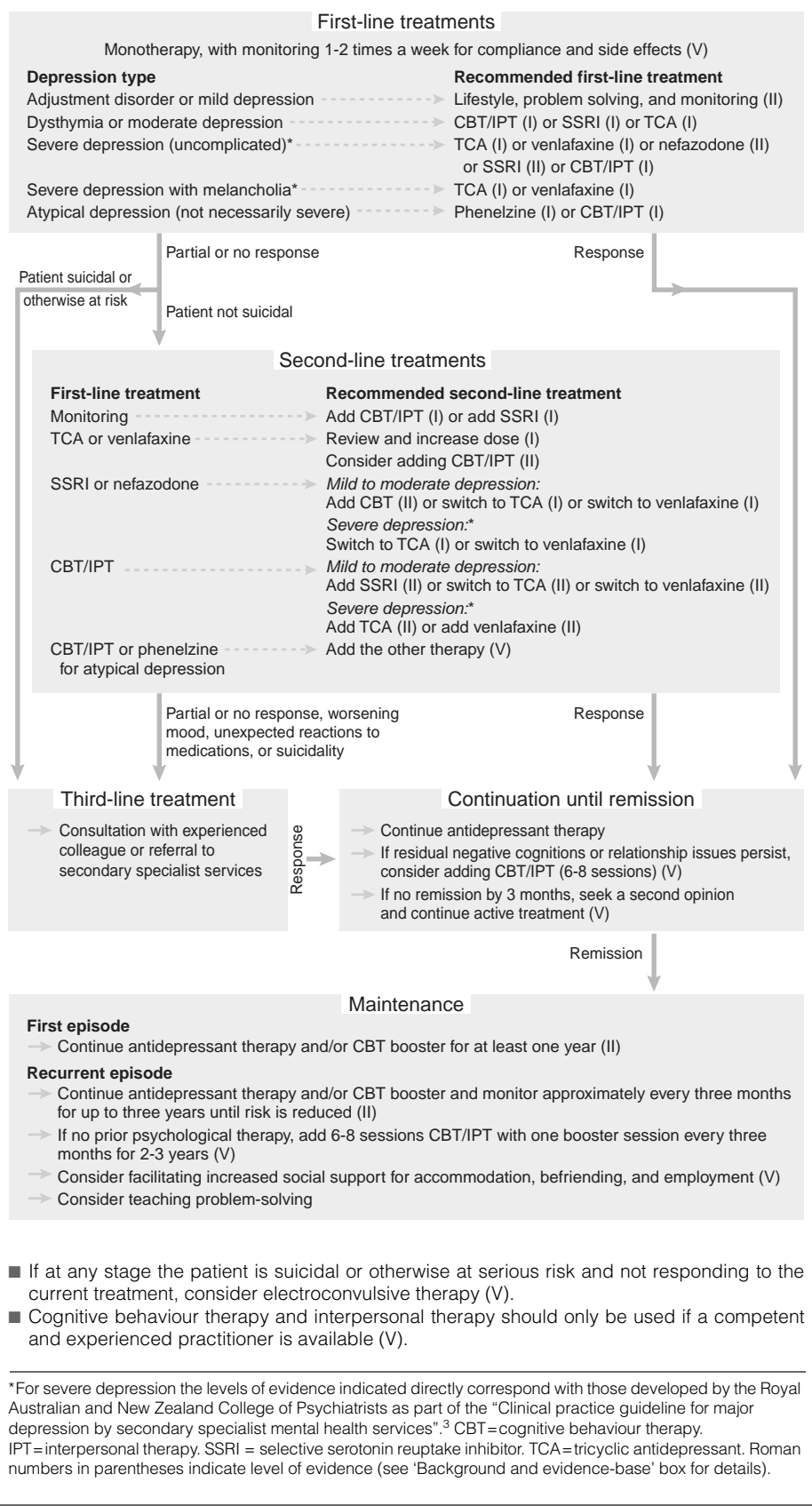
The evidence supports the following treatment recommendations as part of an overall clinical management plan.

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^{120,121}). 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 relapse¹²²⁻¹²⁷) (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^{111,118,128} (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

Pete M Ellis, Psychiatrist, Wellington School of Medicine, University of Otago, New Zealand

Don A R Smith, Psychologist, Wellington School of Medicine, University of Otago, New Zealand

Ian B Hickie, Psychiatrist, School of Psychiatry, University of New South Wales, NSW

John A Bushnell, Psychiatrist, Wellington School of Medicine, University of Otago, New Zealand

Paul Hirini, Psychologist, School of Maori Studies, Te-Putahi-a-Toi, Massey University, New Zealand

Kirsty E D Loudon, Clinical Psychologist, Wellington School of Medicine, University of Otago, New Zealand

Suzy M Stevens, Consumer Advisor, Mental Health Foundation, Auckland, New Zealand

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.¹²⁹ 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^{128,130} (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.

Acknowledgements

Preparation of the guidelines was funded by *beyondblue: the national depression initiative*.

References

1. McLennan W. Mental health and wellbeing: profile of adults, Australia 1997. Canberra: Australian Bureau of Statistics, 1998.
2. Hickie IB, Davenport TA, Hadzi-Pavlovic D, et al. Development of a simple screening tool for common mental disorders in general practice. *Med J Aust* 2001; 175 Suppl Jul 16: S10-S17.
3. Working Party convened by the Royal Australian and New Zealand College of Psychiatry. Clinical practice guideline for major depression by secondary specialist mental health services. 2001. <<http://www.ranzcp.org/cpg/fgdepression16-01-2001.pdf>>. Accessed 17 April 2002.
4. American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder (revision). *Am J Psychiatry* 2000; 157 Suppl 4: 1-45.
5. *beyondblue: the national depression initiative*. <<http://www.beyondblue.org.au>>. Accessed 15 April 2002.
6. National Health and Medical Research Council. Guidelines for the development and implementation of clinical practice guidelines. Canberra: NHMRC, 1995.
7. Agency for Health Care Policy and Research. Treatment of depression: newer pharmacotherapies. Evidence Report/Technology Assessment No. 7. Washington, DC: AHCPR, 1999.
8. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960; 23: 56-62.
9. Andersen G, Vestergaard K, Lauritzen L. Effective treatment of poststroke depression with the selective serotonin reuptake inhibitor citalopram. *Stroke* 1994; 25: 1099-1104.
10. Heiligenstein JH, Tollefson GD, Faries DE. Response patterns of depressed outpatients with and without melancholia: a double-blind, placebo-controlled trial of fluoxetine versus placebo. *J Affect Disord* 1994; 30: 163-173.
11. Mynors-Wallis LM, Gath DH, Lloyd-Thomas AR, et al. Randomised controlled trial comparing problem solving treatment with amitriptyline and placebo for major depression in primary care. *BMJ* 1995; 310: 441-445.
12. Bremner JD. A double-blind comparison of Org 3770, amitriptyline, and placebo in major depression. *J Clin Psychiatry* 1995; 56: 519-525.
13. Brown WA, Arato M, Shrivastava R. Pituitary-adrenocortical hyperfunction and intolerance to fluvoxamine, a selective serotonin uptake inhibitor. *Am J Psychiatry* 1986; 143: 88-90.
14. Cohn JB, Wilcox CS. Low-sedation potential of buspirone compared with alprazolam and lorazepam in the treatment of anxious patients: a double-blind study. *J Clin Psychiatry* 1986; 47: 409-412.
15. Doogan DP, Langdon CJ. A double-blind, placebo-controlled comparison of sertraline and dothiepin in the treatment of major depression in general practice. *Int Clin Psychopharmacol* 1994; 9: 95-100.
16. Fabre L, Birkhimer LJ, Zaborny BA, et al. Fluvoxamine versus imipramine and placebo: a double-blind comparison in depressed patients. *Int Clin Psychopharmacol* 1996; 11: 119-127.

17. Feighner JP, Boyer WF. Paroxetine in the treatment of depression: a comparison with imipramine and placebo. *Acta Psychiatr Scand* 1989; 350 Suppl: 125-129.
18. Lydiard RB, Laird LK, Morton WA Jr, et al. Fluvoxamine, imipramine, and placebo in the treatment of depressed outpatients: effects on depression. *Psychopharmacol Bull* 1989; 25: 68-70.
19. Muijen M, Roy D, Silverstone T, et al. A comparative clinical trial of fluoxetine, mianserin and placebo in depressed outpatients. *Acta Psychiatr Scand* 1988; 78: 384-390.
20. Reimherr FW, Chouinard G, Cohn CK, et al. Antidepressant efficacy of sertraline: a double-blind, placebo- and amitriptyline-controlled, multicenter comparison study in outpatients with major depression. *J Clin Psychiatry* 1990; 51 Suppl B: 18-27.
21. Stark P, Hardison CD. A review of multicenter controlled studies of fluoxetine vs. imipramine and placebo in outpatients with major depressive disorder. *J Clin Psychiatry* 1985; 46: 53-58.
22. Cohn CK, Robinson DS, Roberts DL, et al. Responders to antidepressant drug treatment: a study comparing nefazodone, imipramine, and placebo in patients with major depression. *J Clin Psychiatry* 1996; 57 Suppl 2: 15-18.
23. Elkin I, Shea MT, Watkins JT, et al. National Institute of Mental Health Treatment of Depression Collaborative Research Program. General effectiveness of treatments. *Arch Gen Psychiatry* 1989; 46: 971-982.
24. Fontaine R, Ontiveros A, Elie R, et al. A double-blind comparison of nefazodone, imipramine, and placebo in major depression. *J Clin Psychiatry* 1994; 55: 234-241.
25. Philipp M, Kohnen R, Hiller KO. Hypericum extract versus imipramine or placebo in patients with moderate depression: randomised multicentre study of treatment for eight weeks. *BMJ* 1999; 319: 1534-1538.
26. Rickels K, Schweizer E, Clary C, et al. Nefazodone and imipramine in major depression: a placebo-controlled trial. *Br J Psychiatry* 1994; 164: 802-805.
27. Roth D, Mattes J, Sheehan KH, et al. A double-blind comparison of fluvoxamine, desipramine and placebo in outpatients with depression. *Prog Neuropsychopharmacol Biol Psychiatry* 1990; 14: 929-939.
28. Schweizer E, Feighner J, Mandos LA, et al. Comparison of venlafaxine and imipramine in the acute treatment of major depression in outpatients. *J Clin Psychiatry* 1994; 55: 104-108.
29. Claghorn JL. The safety and efficacy of paroxetine compared with placebo in a double-blind trial of depressed outpatients. *J Clin Psychiatry* 1992; 53 Suppl: 33-35.
30. Dunlop SR, Dornseif BE, Wernicke JF, et al. Pattern analysis shows beneficial effect of fluoxetine treatment in mild depression. *Psychopharmacol Bull* 1990; 26: 173-180.
31. Evans M, Hammond M, Wilson K, et al. Placebo-controlled treatment trial of depression in elderly physically ill patients. *Int J Geriatr Psychiatry* 1997; 12: 817-824.
32. Heiligenstein JH, Tollefson GD, Faries DE. A double-blind trial of fluoxetine, 20 mg, and placebo in out-patients with DSM-III-R major depression and melancholia. *Int Clin Psychopharmacol* 1993; 8: 247-251.
33. Hellerstein DJ, Yanowitch P, Rosenthal J, et al. A randomized double-blind study of fluoxetine versus placebo in the treatment of dysthymia. *Am J Psychiatry* 1993; 150: 1169-1175.
34. Kiev A. A double-blind, placebo-controlled study of paroxetine in depressed outpatients. *J Clin Psychiatry* 1992; 53 Suppl: 27-29.
35. Laughren TP. The review of clinical safety data in a new drug application. *Psychopharmacol Bull* 1989; 25: 5-8.
36. Massana J. Reboxetine versus fluoxetine: an overview of efficacy and tolerability. *J Clin Psychiatry* 1998; 59 Suppl: 8-10.
37. Olie JP, Gunn KP, Katz E. A double-blind placebo-controlled multicentre study of sertraline in the acute and continuation treatment of major depression. *Eur Psychiatry* 1997; 12: 34-41.
38. Rickels K, Amsterdam J, Clary C, et al. A placebo-controlled, double-blind, clinical trial of paroxetine in depressed outpatients. *Acta Psychiatr Scand* 1989; 350 Suppl: 117-123.
39. Smith WT, Glaudin V. A placebo-controlled trial of paroxetine in the treatment of major depression. *J Clin Psychiatry* 1992; 53 Suppl: 36-39.
40. Thase ME, Fava M, Halbreich U, et al. A placebo-controlled, randomized clinical trial comparing sertraline and imipramine for the treatment of dysthymia. *Arch Gen Psychiatry* 1996; 53: 777-784.
41. Khan A, Upton GV, Rudolph RL, et al. The use of venlafaxine in the treatment of major depression and major depression associated with anxiety: a dose-response study. Venlafaxine Investigator Study Group. *J Clin Psychopharmacol* 1998; 18: 19-25.
42. Rudolph RL, Fabre LF, Feighner JP, et al. A randomized, placebo-controlled, dose-response trial of venlafaxine hydrochloride in the treatment of major depression. *J Clin Psychiatry* 1998; 59: 116-122.
43. Rudolph RL, Feiger AD. A double-blind, randomized, placebo-controlled trial of once-daily venlafaxine extended release (XR) and fluoxetine for the treatment of depression. *J Affect Disord* 1999; 56: 171-181.
44. Halikias JA. Org 3770 (mirtazapine) versus trazodone: a placebo controlled trial in depressed elderly patients. *Hum Psychopharmacol* 1995; 10 Suppl 2: 125-133.
45. Smith WT, Glaudin V, Panagides J, et al. Mirtazapine vs. amitriptyline vs. placebo in the treatment of major depressive disorder. *Psychopharmacol Bull* 1990; 26: 191-196.
46. Feighner J, Targum SD, Bennett ME, et al. A double-blind, placebo-controlled trial of nefazodone in the treatment of patients hospitalized for major depression. *J Clin Psychiatry* 1998; 59: 246-253.
47. De Jong R, Treiber R, Henrich G. Effectiveness of two psychological treatments for inpatients with severe and chronic depression. *Cognitive Ther Res* 1988; 10: 645-663.
48. Jarrett RB, Schaffer M, McIntire D, et al. Treatment of atypical depression with cognitive therapy or phenelzine: a double-blind, placebo-controlled trial. *Arch Gen Psychiatry* 1999; 56: 431-437.
49. Stewart JW, Garfinkel R, Nunes EV, et al. Atypical features and treatment response in the National Institute of Mental Health Treatment of Depression Collaborative Research Program. *J Clin Psychopharmacol* 1998; 18: 429-434.
50. Guy W, Wilson WH, Ban TA, et al. A double-blind clinical trial of fluvoxamine and imipramine in patients with primary depression. *Psychopharmacol Bull* 1984; 20: 73-78.
51. Nathan RS, Perel JM, Pollock BG, et al. The role of neuropharmacologic selectivity in antidepressant action: fluvoxamine versus desipramine. *J Clin Psychiatry* 1990; 51: 367-372.
52. Ohrberg S, Christiansen PE, Severin B, et al. Paroxetine and imipramine in the treatment of depressive patients in psychiatric practice. *Acta Psychiatr Scand* 1992; 86: 437-444.
53. Tollefson GD, Greist JH, Jefferson JW, et al. Is baseline agitation a relative contraindication for a selective serotonin reuptake inhibitor: a comparative trial of fluoxetine versus imipramine. *J Clin Psychopharmacol* 1994; 14: 385-391.
54. Duarte A, Mikkelsen H, Delini-Stula A. Moclobemide versus fluoxetine for double depression: a randomized double-blind study. *J Psychiatr Res* 1996; 30: 453-458.
55. Kragh-Sorensen P, Muller B, Andersen JV, et al. Moclobemide versus clomipramine in depressed patients in general practice. A randomized, double-blind, parallel, multicenter study. *J Clin Psychopharmacol* 1995; 15 Suppl 2: 24-30.
56. Reynaert C, Parent M, Mirel J, et al. Moclobemide versus fluoxetine for a major depressive episode. *Psychopharmacology* 1995; 118: 183-187.
57. Mynors-Wallis LM, Gath DH, Day A, et al. Randomised controlled trial of problem solving treatment, antidepressant medication, and combined treatment for major depression in primary care. *BMJ* 2000; 320: 26-30.
58. Chilvers C, Dewey M, Fielding K, et al. Antidepressant drugs and generic counselling for treatment of major depression in primary care: randomised trial with patient preference arms. *BMJ* 2001; 322: 772-775.
59. Battegay R, Hager M, Rauchfleisch U. Double-blind comparative study of paroxetine and amitriptyline in depressed patients of a university psychiatric outpatient clinic (pilot study). *Neuropsychobiology* 1985; 13: 31-37.
60. Beasley CM Jr, Holman SL, Potvin JH. Fluoxetine compared with imipramine in the treatment of inpatient depression. A multicenter trial. *Ann Clin Psychiatry* 1993; 5: 199-207.
61. Beasley CM Jr, Saylor ME, Potvin JH. Fluoxetine versus amitriptyline in the treatment of major depression: a multicenter trial. *Int Clin Psychopharmacol* 1993; 8: 143-149.
62. Berzewski H, Van Moffaert M, Gagiano CA. Efficacy and tolerability of reboxetine compared with imipramine in a double-blind study in patients suffering from major depressive episodes. *Eur Neuropsychopharmacol* 1997; 7 Suppl 1: 37-47.
63. Bignamini A, Rapisarda V. A double-blind multicentre study of paroxetine and amitriptyline in depressed outpatients. Italian Paroxetine Study Group. *Int Clin Psychopharmacol* 1992; 6 Suppl 4: 37-41.
64. Bouchard JM, Delaunay J, Delisle JP, et al. Citalopram versus maprotiline: a controlled, clinical multicentre trial in depressed patients. *Acta Psychiatr Scand* 1987; 76: 583-592.
65. Bowden CL, Schatzberg AF, Rosenbaum A, et al. Fluoxetine and desipramine in major depressive disorder. *J Clin Psychopharmacol* 1993; 13: 305-311.
66. Feighner JP. A comparative trial of fluoxetine and amitriptyline in patients with major depressive disorder. *J Clin Psychiatry* 1985; 46: 369-372.
67. Fawcett J, Zajecka JM, Kravitz HM, et al. Fluoxetine versus amitriptyline in adult outpatients with major depression. *Current Therapeutic Research* 1989; 45: 821-831.
68. Byerley WF, Reimherr FW, Wood DR, et al. Fluoxetine, a selective serotonin uptake inhibitor, for the treatment of outpatients with major depression. *J Clin Psychopharmacol* 1988; 8: 112-115.
69. Cohn JB, Wilcox C. A comparison of fluoxetine, imipramine, and placebo in patients with major depressive disorder. *J Clin Psychiatry* 1985; 46: 26-31.
70. Danish University Antidepressant Group. Paroxetine: a selective serotonin reuptake inhibitor showing better tolerance, but weaker antidepressant effect than clomipramine in a controlled multicenter study. *J Affect Disord* 1990; 18: 289-299.
71. de Wilde J, Mertens C, Overo KF, et al. Citalopram versus mianserin. A controlled, double-blind trial in depressed patients. *Acta Psychiatr Scand* 1985; 72: 89-96.
72. Dorman T. Sleep and paroxetine: a comparison with mianserin in elderly depressed patients. *Int Clin Psychopharmacol* 1992; 6 Suppl 4: 53-58.
73. Dowling B, Webb MGT, Halpin CM, et al. Fluoxetine: a comparative study with dothiepin. *Ir J Psychiatry* 1990; Spring: 3-7.

74. Fournier JP, Lane RM, Chouinard DB, et al. A double-blind comparison of sertraline and imipramine in outpatients with major depression. *Hum Psychopharmacol* 1997; 12: 203-215.
75. Guillibert E, Pelicier Y, Archambault JC, et al. A double-blind, multicentre study of paroxetine versus clomipramine in depressed elderly patients. *Acta Psychiatr Scand* 1989; 350 Suppl: 132-134.
76. Hoehn-Saric R, Ninan P, Black DW, et al. Multicenter double-blind comparison of sertraline and desipramine for concurrent obsessive-compulsive and major depressive disorders. *Arch Gen Psychiatry* 2000; 57: 76-82.
77. Hutchinson DR, Tong S, Moon CA, et al. Paroxetine in the treatment of elderly depressed patients in general practice: a double-blind comparison with amitriptyline. *Int Clin Psychopharmacol* 1992; 6 Suppl 4: 43-51.
78. Keegan D, Bowen RC, Blackshaw S, et al. A comparison of fluoxetine and amitriptyline in the treatment of major depression. *Int Clin Psychopharmacol* 1991; 6: 117-124.
79. Keller MB, Gelenberg AJ, Hirschfeld RM, et al. The treatment of chronic depression, part 2: a double-blind, randomized trial of sertraline and imipramine. *J Clin Psychiatry* 1998; 59: 598-607.
80. Kerkhofs M, Rielaeert C, de Maertelaer V, et al. Fluoxetine in major depression: efficacy, safety and effects on sleep polygraphic variables. *Int Clin Psychopharmacol* 1990; 5: 253-260.
81. Ko HC, Lu RB, Shiah IS, et al. Plasma free 3-methoxy-4-hydroxyphenylglycol predicts response to fluoxetine. *Biol Psychiatry* 1997; 41: 774-781.
82. Levine S, Deo R, Mahadevan K. A comparative trial of a new antidepressant, fluoxetine. *Int Clin Psychopharmacol* 1989; 4 Suppl 1: 41-45.
83. Moon CAL, Jago W, Wood K, et al. A double-blind comparison of sertraline and clomipramine in the treatment of major depressive disorder and associated anxiety in general practice. *J Psychopharmacol* 1994; 8: 171-176.
84. Moon CA, Vince M. Treatment of major depression in general practice: a double-blind comparison of paroxetine and lofepramine. *Br J Clin Pract* 1996; 50: 240-244.
85. Moller HJ, Berzowski H, Eckmann F, et al. Double-blind multicenter study of paroxetine and amitriptyline in depressed inpatients. *Pharmacopsychiatry* 1993; 26: 75-78.
86. Nelson JC, Kennedy JS, Pollock BG, et al. Treatment of major depression with nortriptyline and paroxetine in patients with ischemic heart disease. *Am J Psychiatry* 1999; 156: 1024-1028.
87. Nielsen BM, Behnke K, Arup P, et al. A comparison of fluoxetine and imipramine in the treatment of outpatients with major depressive disorder. *Acta Psychiatr Scand* 1993; 87: 269-272.
88. Ravindran AV, Judge R, Hunter BN, et al. A double-blind, multicenter study in primary care comparing paroxetine and clomipramine in patients with depression and associated anxiety. Paroxetine Study Group. *J Clin Psychiatry* 1997; 58: 112-118.
89. Robertson MM, Abou-Saleh MT, Harrison DA, et al. Double blind comparative trial of fluoxetine and lofepramine in major depression. *J Pharmacol* 1994; 115: 261-264.
90. Roose SP, Laghrissi-Thode F, Kennedy JS, et al. Comparison of paroxetine and nortriptyline in depressed patients with ischemic heart disease. *JAMA* 1998; 279: 287-291.
91. Roose SP, Glassman AH, Attia E, et al. Comparative efficacy of selective serotonin reuptake inhibitors and tricyclics in the treatment of melancholia. *Am J Psychiatry* 1994; 151: 1735-1739.
92. Rosenberg C, Damsbo N, Fuglum E, et al. Citalopram and imipramine in the treatment of depressive patients in general practice. A Nordic multicentre clinical study. *Int Clin Psychopharmacol* 1994; 9 Suppl 1: 41-48.
93. Schnyder U, Koller-Leiser A. A double-blind, multicentre study of paroxetine and maprotiline in major depression. *Can J Psychiatry* 1996; 41: 239-244.
94. Staner L, Kerkhofs M, Detroux D, et al. Acute, subchronic and withdrawal sleep EEG changes during treatment with paroxetine and amitriptyline: a double-blind randomized trial in major depression. *Sleep* 1995; 18: 470-477.
95. Stuppaek CH, Geretsegger C, Whitworth AB, et al. A multicenter double-blind trial of paroxetine versus amitriptyline in depressed inpatients. *J Clin Psychopharmacol* 1994; 14: 241-246.
96. Tignol J, Stoker MJ, Dunbar GC. Paroxetine in the treatment of melancholia and severe depression. *Int Clin Psychopharmacol* 1992; 7: 91-94.
97. Van Moffaert M, Pregaldien JL, Von Frenckell R, et al. A double-blind comparison of nefazodone and imipramine in the treatment of depressed patients. *New Trends Exp Clin Psychiatry* 1994; 10: 85-87.
98. Costa e Silva J. Randomized, double-blind comparison of venlafaxine and fluoxetine in outpatients with major depression. *J Clin Psychiatry* 1998; 59: 352-357.
99. Dierckx M, Ravizza L, Realini R, et al. A double-blind comparison of venlafaxine and fluoxetine for treatment of major depression in outpatients. *Prog Neuropsychopharmacol Biol Psychiatry* 1996; 20: 57-71.
100. Gentil V, Kerr-Correa F, Moreno R, et al. Double-blind comparison of venlafaxine and amitriptyline in outpatients with major depression with or without melancholia. *J Psychopharmacol* 2000; 14: 61-66.
101. Lecrubier Y, Bourin M, Moon CA, et al. Efficacy of venlafaxine in depressive illness in general practice. *Acta Psychiatr Scand* 1997; 95: 485-493.
102. Poirier MF, Boyer P. Venlafaxine and paroxetine in treatment-resistant depression. Double-blind, randomised comparison. *Br J Psychiatry* 1999; 175: 12-16.
103. Tylee A, Beaumont G, Bowden MW, et al. A double-blind, randomised, 12-week comparison study of the safety and the efficacy of venlafaxine and fluoxetine in moderate to severe major depression in general practice. *Prim Care Psychiatry* 1997; 3: 51-58.
104. Clerc GE, Ruimy P, Verdeau-Palles J. A double-blind comparison of venlafaxine and fluoxetine in patients hospitalized for major depression and melancholia. The Venlafaxine French Inpatient Study Group. *Int Clin Psychopharmacol* 1994; 9: 139-143.
105. Zivkov M, De Jongh GD. Mirtazapine vs amitriptyline: a 6-week randomised double-blind multicentre trial in hospitalised depressed patients. *Hum Psychopharmacol*. In press.
106. Rush AJ, Armitage R, Gillin JC, et al. Comparative effects of nefazodone and fluoxetine on sleep in outpatients major depressive disorder. *Biol Psychiatry* 1998; 44: 3-14.
107. Williams R, Edwards RA, Newburn GM, et al. A double-blind comparison of moclobemide and fluoxetine in the treatment of depressive disorders. *Int Clin Psychopharmacol* 1993; 7: 155-158.
108. Ramaekers JG, Ansseau M, Muntjewerff ND, et al. Considering the P450 cytochrome system as determining combined effects of antidepressants and benzodiazepines on actual driving performance of depressed outpatients. *Int Clin Psychopharmacol* 1997; 12: 159-169.
109. Geerts S, Bruynooghe F, De Cuyper H, et al. Moclobemide versus fluoxetine for major depressive episodes. *Clin Neuropharmacol* 1994; 17 Suppl 1: 50-57.
110. Lapierre YD, Joffe R, McKenna K, et al. Moclobemide versus fluoxetine in the treatment of major depressive disorders in adults. *J Psychiatry Neurosci* 1997; 22: 118-126.
111. Keller MB, McCullough JP, Klein DN, et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. *N Engl J Med* 2000; 342: 1462-1470.
112. Dunner DL, Schmalting KB, Hendrickson H, et al. Cognitive therapy versus fluoxetine in the treatment of dysthymic disorder. *Depression* 1996; 4: 34-41.
113. Hollon SD, DeRubeis RJ, Evans MD, et al. Cognitive therapy and pharmacotherapy for depression. Singly and in combination. *Arch Gen Psychiatry* 1992; 49: 774-781.
114. Murphy GE, Simons AD, Wetzel RD, et al. Cognitive therapy and pharmacotherapy. Singly and together in the treatment of depression. *Arch Gen Psychiatry* 1984; 41: 33-41.
115. Hirschfeld RMA. Care of the sexually active depressed patient. *J Clin Psychiatry* 1999; 60 Suppl 17: 32-35.
116. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Measurement* 1977; 1: 385-401.
117. Thase ME. Redefining antidepressant efficacy toward long-term recovery. *J Clin Psychiatry* 1999; 60 Suppl 6: 15-19.
118. Scott J. Treatment of chronic depression [letter]. *N Engl J Med* 2000; 342: 1518-1520.
119. MacKenzie KR, Leszcz M, Abbas A, et al. Guidelines for the psychotherapies in comprehensive psychiatric care: a discussion paper. Working Group 2 of the Canadian Psychiatric Association Psychotherapies Steering Committee. *Can J Psychiatry* 1999; 44 Suppl 1: 4S-17S.
120. Oei TPS, Yeoh AEO. Pre-existing antidepressant medication and the outcome of group cognitive-behavioural therapy. *Aust N Z J Psychiatry* 1999; 33: 70-76.
121. Thase ME, Friedman ES. Is psychotherapy an effective treatment for melancholia and other severe depressive states? *J Affect Disord* 1999; 54: 1-19.
122. Hollon SD, Shelton RC, Loosen PT. Cognitive therapy and pharmacotherapy for depression. *J Consult Clin Psychol* 1991; 59: 88-99.
123. Antonuccio DO, Danton WG, DeNelsky GY. Psychotherapy versus medication for depression: challenging the conventional wisdom with data. *Professional Psychol Res Pract* 1995; 26: 574-585.
124. Gloaguen V, Cottraux J, Cucherat M, Blackburn IM. A meta-analysis of the effects of cognitive therapy in depressed patients. *J Affect Disord* 1998; 49: 59-72.
125. Fava GA, Ottolini F, Ruini C. The role of cognitive behavioural therapy in the treatment of unipolar depression [letter]. *Acta Psychiatr Scand* 1999; 99: 394-396.
126. DeRubeis RJ, Gelfand LA, Tang TZ, Simons AD. Medications versus cognitive behaviour therapy for severely depressed outpatients: mega-analysis of four randomized comparisons. *Am J Psychiatry* 1999; 156: 1007-1013.
127. Balslev Jorgensen M, Dam H, Bolwig TG. The efficacy of psychotherapy in non-bipolar depression: a review. *Acta Psychiatr Scand* 1998; 98: 1-13.
128. Paykel ES, Scott J, Teasdale JD, et al. Prevention of relapse in residual depression by cognitive therapy. *Arch Gen Psychiatry* 1999; 56: 829-835.
129. Frank E, Kupfer DJ, Perel JM, et al. Three-year outcomes for maintenance therapies in recurrent depression. *Arch Gen Psychiatry* 1990; 47: 1093-1099.
130. Jarrett RB, Kraft D, Doyle J, et al. Preventing recurrent depression using cognitive therapy with and without a continuation phase: a randomized clinical trial. *Arch Gen Psychiatry* 2001; 58: 381-388. □