Prevalence and outcome of partial remission in depression

Richard Tranter, MB ChB; Claire O'Donovan, MB; Praful Chandarana, MD; Sidney Kennedy, MD

Tranter — North Wales Psychiatry Training Rotation, Wales, UK; O'Donovan — Department of Psychiatry, Dalhousie University, Halifax, NS; Chandarana — Department of Psychiatry, University of Western Ontario, London, Ont.; Kennedy — Department of Psychiatry, University of Toronto, Toronto, Ont.

The goal of treatment of major depression should be full remission. Many patients, however, fail to achieve or maintain symptom-free status. Residual depressive symptoms are common, even where there has been a robust response to antidepressant therapy. In clinical studies, approximately one-third of patients achieve a full remission, one-third experience a response and one-third are nonresponders. Partial remission is characterized by the presence of poorly defined residual symptoms. These symptoms typically include depressed mood, psychic anxiety, sleep disturbance, fatigue and diminished interest or pleasure. It is currently unclear which factors predict partial remission. However, it is clear that residual symptoms are powerful predictors of relapse, with relapse rates 3–6 times higher in patients with residual symptoms than in those who experience full remission. Residual symptoms are also associated with more medical and psychiatric visits, increased public assistance, disability benefits, thoughts of and attempts at suicide and chronicity. The risk of stroke and coronary events is also higher in patients with residual depressive symptoms. The substantial proportion of patients who achieve only partial remission has traditionally been neglected in antidepressant trials. Given that residual symptoms may relate, in part, to an incompatibility between patient and treatment, further research is needed to predict a better match. These symptoms are a clinically relevant state of illness, and the correct choice of initial antidepressant treatment should offer the greatest chance of achieving full remission.

Le traitement d'une dépression majeure devrait viser la rémission complète. Beaucoup de patients ne réussissent toutefois pas à se débarrasser définitivement des symptômes. Les symptômes résiduels de la dépression sont courants, même lorsque la thérapie aux antidépresseurs a produit une réponse solide. Des études cliniques ont révélé qu'environ le tiers des patients parviennent à une rémission compiète, le tiers réagissent et le tiers ne réagissent pas. La rémission partielle est caractérisée par la présence de symptômes résiduels mal définis. Ces symptômes comprennent habituellement la dépression de l'humeur, l'anxiété psychique, les troubles du sommeil, la fatigue et une baisse de l'intérêt ou du plaisir. Les facteurs prédicteurs d'une rémission partielle ne sont pas clairs actuellement. Il est toutefois clair que les symptômes résiduels sont des prédicteurs puissants de rechute et les taux de rechute sont de trois à six fois plus élevés chez les patients qui présentent des symptômes résiduels que chez ceux qui connaissent une

Correspondence to: Dr. Richard Tranter, Department of Psychological Medicine, Hergest Unit, North West Wales NHS Trust, Bangor, Gwynedd LL57 2PW; richard.tranter@ntlworld.com

Medical subject headings: antidepressive agents; behavioral symptoms; cognitive therapy; depressive disorder; drug therapy; psychiatric status rating scales; psychotherapy; recurrence; remission induction; treatment outcome.

J Psychiatry Neurosci 2002;27(4):241-7.

Submitted Sep. 10, 2001
Revised May 15, 2002
Accepted May 24, 2002

rémission complète. On établit aussi un lien entre les symptômes résiduels et l'augmentation du nombre de consultations de médecins et de psychiatres, de l'aide publique, des prestations d'invalidité, des pensées suicidaires, des tentatives de suicide et de la chronicité. Le risque d'accident vasculaire cérébral et d'incident coronarien est aussi plus élevé chez les patients qui présentent des symptômes résiduels de dépression. Les études sur les antidépresseurs ont toujours négligé la proportion importante de patients qui parviennent à une rémission partielle seulement. Étant donné qu'il peut y avoir un lien partiel entre les symptômes résiduels et une incompatibilité entre le patient et le traitement, des recherches plus poussées s'imposent pour prévoir une meilleure correspondance. Ces symptômes sont un état morbide pertinent sur le plan clinique et le bon choix du traitement initial aux antidépresseurs devrait offrir la meilleure chance de produire une rémission complète.

Introduction

Despite many effective therapeutic strategies, depression continues to be a highly prevalent, disabling and costly condition.[1-3] The World Health Organization identifies unipolar major depression as the leading cause of disability in the world.[4] Although most patients experiencing an episode of depression undergo some acute improvement after treatment, long-term outcomes remain disappointing.[5,6] Although full remission is the goal of treatment,[7] many patients fail to achieve or maintain symptom-free states.[8] The exact nature and origin of residual symptoms is currently debated, but their tremendous impact on outcomes such as future relapse, morbidity and mortality is clear. A better understanding of residual symptoms may inform future treatment choices in depression and ultimately improve prognosis.

For this review, a MEDLINE search was conducted using the terms "residual symptoms of depression," "partial remission from depression" and "subsyndromal depression." Further key references were then identified from the initial review papers. As well as focusing on current theories regarding residual symptoms, this review will also highlight inadequacies in the existing literature.

Partial remission

The optimal outcome in the treatment of major depression should be the virtual elimination of symptoms and a return to a premorbid level of functioning. However, clinical depression with or without treatment can result in various negative outcomes including chronicity, relapse and recurrence.[5,9] Definitions of response, remission, relapse and recurrence are consistent with those described in the introductory article to this series (i.e., those of Frank et al[10]). Another important adverse outcome for major depression is partial remission with residual symptoms. Frank and colleagues[10] defined partial remission as a period of sufficient improvement such that an individual no longer fulfills the criteria for major depressive disorder (MDD) but continues to evidence more than minimal symptoms. Partial remission with minimal or residual symptoms has been defined in numerous ways in the literature, most commonly using the Hamilton Rating Scale for Depression (HAM-D) (Table 1).[5,11-15] Other tools have also been used to evaluate residual symptoms such as the Clinical Interview for Depression (CID) and the Montgomery–Asberg Depression Rating Scale (MADRS), but to facilitate comparisons, this review will focus on studies using the HAM-D.

Subsyndromal or subthreshold depression, a related phenomenon (less than threshold symptoms for MDD), is a much broader category as it includes spontaneous depressive symptoms in community studies, prodromal symptoms and residual symptoms.[16,17] Although the literature suggests similarities to partial remission (e.g., negative impact, increased episodes of depression), this concept is outside the scope of this review.

The existence of partial remission has been widely recognized, but its significance in clinical practice has not.[18] Clinical trials report rates of response (50% reduction in symptoms), nonresponse and, in a minority of studies, remission (HAM-D ≤ 7).[10] Partial remission and residual symptoms are not reported in most trials designed to look at the efficacy of antidepressant strategies. In addition, most drug trials last 6–8 weeks, not long enough for most patients to achieve remission.

In most studies specifically designed to determine the nature and prevalence of partial remission, patients are considered to have residual symptoms if they responded to therapy but had a HAM-D score of 8 or

more (Table 1).[5] However, it has now been suggested that patients who achieve full remission, as defined by even the most conservative criteria, may continue to have residual symptoms.[10,13] Estimating the impact of residual symptoms is further limited by the fact that there are few known baseline HAM-D scores for the general population. Therefore, accurate comparisons are not possible.

Prevalence of residual symptoms

Many studies have reported on the prevalence of symptomatic patients after various pharmacotherapies and psychotherapies, both prospectively and naturalistically, in psychiatric clinics and in primary care.[10,11,13,19–22] However, each study has a unique method for reporting residual symptoms, and the patient populations, treatment modalities and time periods differ. Although trials of antidepressant treatment typically report response rates in the order of 70%–80%, longer-term follow-up studies have shown that no more than a third of patients achieve full remission from their depressive symptoms.[20] The report by Kupfer and Spiker[23] is representative of most studies looking at long-term response to treatments for depression, suggesting the "rule of thirds" may apply: a third of patients achieve complete remission, a third do not respond and a third show partial remission.[23]

In a long-term outcome study over 4 years, 50% of patients who had been treated with amitriptyline and psychotherapy experienced residual symptoms.[19] Similarly, in a 4-year follow-up study of elderly depressed patients, 38% experienced residual symptoms 1 year after remission and 20% had residual symptoms after 4 years.[21] Paykel and colleagues,[5] who followed a cohort of 64 inpatients and outpatients who had achieved partial remission during treatment for major depression, reported that after 15 months, 32% of patients exhibited residual symptoms. Finally, in a 10-year follow-up, the National Institute of Mental Health (NIMH) Collaborative Depression Study Group reported that 34% of patients were in partial remission.[22]

Patients who meet remission criteria may still experience residual symptoms. In a study of subjects who were in full remission (i.e., HAM-D ≤ 7) after treatment with fluoxetine (20 mg for 8 weeks), more than 80% of patients had 1 or more symptoms, and more than 30% had more than 3 residual symptoms of MDD.[13]

Nature of residual symptoms

In a study of patients who remained partial responders to antidepressant therapy (HAM-D score 8–18), 47% reported depressed mood, impairment of work and activities, psychic anxiety or sexual dysfunction, to at least a moderate degree.[5] Symptoms that are more commonly associated with severe depression, including late insomnia, retardation, agitation, hypochondriasis, weight loss and loss of insight were less common. The most persistent residual symptoms reported in a study of elderly patients (mean age 67 yr) during the continuation phase of treatment were apathy, anxiety (both psychological and somatic), anergia, insomnia, feelings of guilt and loss of libido.[14] Although sexual

Table 1: Definitions of partial remission and residual symptoms reported in clinical trials, as compared with the conceptual definitions proposed by Frank et al[10]

Study	Sample	Age	Definition of partial remission	Residual symptoms reported
Frank et al[10] Conceptual definition	—	—	HAM-D > 7 for 2 wks	No longer fully symptomatic, continued evidence of more than minimal symptoms
Thase et al[13]	50 outpatients	Mean 37.3 (SD 9.0) yr	HAM-D 6–10 for 2 wks	Not reported
Paykel et al[5]	64 inpatients and outpatients	Range 18–64 yr	HAM-D 8–18	Depressed mood, psychic anxiety, sexual dysfunction, impairment of work and activities
Opdyke et al[14]	105 outpatients	> 67 yr	HAM-D ≤ 10 for 3 wks	Depressed mood, psychic anxiety, somatic anxiety, sexual dysfunction, guilt, anergia, insomnia
Nierenberg et al[11]	215 outpatients	Mean 40.5 (SD 10.3) yr	HAM-D 8–15	Insomnia, fatigue, decreased interest and pleasure
Simon[11]	225 outpatients	Range 18–80 yr	HAM-D ≥ 7	Not reported

Note: HAM-D = Hamilton Rating Scale for Depression, SD = standard deviation.

dysfunction was reported in some studies surveyed, drug side effects were not systematically excluded from residual symptom scores.[5,14]

The 3 most common residual symptoms reported in a study of patients in full remission were sleep disturbances (44%), fatigue (38%) and diminished interest or pleasure (27%).[13] Depressed mood and suicidal ideation were rarely reported. In another study of patients in full remission, the most common residual symptoms were generalized and somatic anxiety and irritability.[24] When patients in remission were compared with a group of volunteers who had never been depressed, they demonstrated significantly more problems with social function, problem solving and dysfunctional attitudes.[25]

Various models have been proposed in an attempt to explain the cause of residual symptoms. A "vulnerability" model suggests that certain pre-existing personality traits are a risk factor for depression and that these traits persist after recovery.[26] In contrast, the "scar" model proposes that depressive episodes cause lasting changes in personality.[27] Several investigators have reported that neuroticism-like personality factors predispose to the development of major depression,[28] whereas extroversion-like factors have been associated with a better response to therapy.[26,29] This suggests that in some patients, the presence of "residual symptoms" may represent a return to baseline personality characteristics, which are also those that predispose to depressive illness. Alternatively, residual symptoms may represent persistent illness; that is, the original illness continuing in a milder form.[5]

Predictors of residual symptoms

Attempts to define predictors of partial and full response to antidepressant therapies have yielded conflicting results in terms of baseline severity,[5,13,30] personality traits[5,14] and the impact of life events.[5,13,14] Paykel's group investigated a number of patient characteristics and found that only severity of illness was a predictor of residual symptoms.[5,30] Conversely, for patients in "full remission" (HAM-$D_{17} \leq 6$), Nierenberg and colleagues[13] reported that the presence of residual symptoms was not predicted by baseline severity of depression. Some studies have found no relation between residual symptoms and life events.[5,13] However, Opdyke et al[14] reported that residual symptoms during continuation treatment in elderly patients who were in full remission (i.e., HAM-D_{17} 10 or less) were observed more often in subjects with associated severe life events or ongoing major stressors.[14] Similarly, personality traits have been associated with residual symptoms in some studies but not in others.[5,14]

No relations have been found between residual symptoms and sociodemographic factors, family and personal history, follow-up care, comorbid conditions, chronic medical burden, social support or past or present illnesses.[5,13,14] In addition, residual symptoms are prevalent, not only in patients who receive psychotherapy, but also in those treated with pharmacotherapy.[12]

Overall, residual symptoms cannot be accurately predicted by age, sex, marital status, number of prior episodes, duration of the current episode, treatment courses or comorbid conditions, but the severity of depression, life stressors and personality dimensions have some predictive value.

Residual symptoms and relapse

Relapse and recurrence are important and, unfortunately, frequent long-term outcomes in the management of patients with depression. The presence of residual symptoms has been associated with a significant increased risk of relapse after treatment with either pharmacotherapy or psychotherapy.[5,12,31–33]

Thase and colleagues[12] found that relapse occurred in 52% of the patients who had a partial response to cognitive therapy (i.e., HAM-D 6–10 for 2 consecutive weeks) but occurred in only 9% of those who had a full response to treatment (i.e., HAM-D ≤ 6 for 8 consecutive weeks).[12] In Paykel's study of those who had responded to treatment (i.e., HAM-D 8–18), 76% of those with residual symptoms, as opposed to 25% of those without, relapsed over the 12- to 15-month follow-up period.[5]

In the NIMH Collaborative Depression Study, patients with (n = 82) or without (n = 155) residual depressive symptoms after treatment were followed naturalistically for 10 years or longer.[32] Patients who had residual symptoms relapsed 3 times faster than patients who achieved full remission. A history of recurrent episodes has also been associated with higher relapse rates, but, in this study, the risk for relapse associated with residual symptoms was significantly greater (odds ratio 3.65) than that associated with a history of recurrent MDD (odds ratio 1.64). Partial remission was still highly predictive of relapse in this

study, despite the more stringent criteria for full remission than those proposed by Frank and colleagues.[10]

In a 1-year follow-up of patients who had received treatment for the index episode of unipolar depression, 50% relapsed;[31] those who relapsed showed higher levels of residual symptoms and Clinical Global Impressions Scale scores that described greater impairment. Neither the HAM-D score at index episode nor at recovery were predictive of relapse. In another study, patients who received psychotherapy (n = 20) to reduce residual symptoms had lower rates of relapse than those who did not (n = 20) after 2 years (15% v. 35%, $p \geq 0.27$), 4 years (35% v. 75%, $p < 0.05$) and 6 years (50% v. 75%, $p = 0.06$).[24,32,34] However, the differences were significant at 4 years only.[34]

A subset analysis compared relapse rates of patients with more severe residual symptoms (HAM-D > 12) with those with milder symptoms (HAM-D 8–12). Surprisingly, the rate of relapse was higher among patients with milder symptoms (90%) compared with those with severe symptoms (57%).[5] It is unknown whether relapse is related to specific symptoms or to the number of symptoms.

The importance of partial remission as a prognostic factor after treatment of depression appears to be independent of the treatment modality adopted. Residual symptoms appear to predict relapse after treatment with pharmacotherapy[35] or psychotherapy.[12,36]

The costs of residual and untreated symptoms

In addition to a higher risk of relapse, residual symptoms are associated with a number of other negative outcomes. Residual symptoms after recovery from depression are associated with more medical and psychiatric visits, emergency room use, psychiatric hospital admissions, increased public assistance, disability benefits, thoughts of suicide and attempted suicide.[2,22] Chronicity is also increased in patients with residual symptoms. A 12-year follow-up of patients after their first major depressive episode demonstrated that those with residual symptoms during recovery had more severe and chronic future courses.[37]

Untreated depressive symptoms also predict future cardiovascular disease and stroke. The Montreal heart studies demonstrated that the risk of cardiovascular mortality after myocardial infarction was significantly increased in patients with a score 10 or more on the Beck Depression Inventory (OR was 3.0 at 12 mo and 7.82 at 18 mo).[38,39] Depression was identified in over 40% of patients with unstable angina and was associated with a significantly increased risk of cardiac death or nonfatal myocardial infarction at 1 year, even after controlling for other significant prognostic factors (adjusted OR 6.73).[40] The Stockholm Female Coronary Risk Study included 292 women, aged 30–65 years, who had been admitted for an acute coronary event between 1991 and 1994.[41] After 5 years of follow-up, 35% of the women who lacked social integration and had 2 or more depressive symptoms had experienced a relapse of their coronary disease, recurrent acute myocardial infarction or cardiovascular death compared with only 9% of the women who were free of depressive symptoms and had good social integration. In a population-based cohort of 6095 adults, depressive symptoms were also found to be predictive of stroke.[42] After adjustment for other risk factors, the presence of self-reported depressive symptoms was associated with a relative risk of stroke of 1.73.

Management of residual symptoms

Residual symptoms are a tremendous economic burden to the health care system and represent a clinically relevant state of illness in people who suffer from MDD. Therefore, it is important to identify treatment strategies that minimize the incidence of residual depressive symptoms. The drug selected for initial treatment should offer the best chance to induce a full remission. Data suggest that amitriptyline and venlafaxine may offer higher rates of full remission.[42–45] Unfortunately, a relatively high incidence of adverse events limits the routine use of the tricyclic antidepressants. It should also be noted that the meta-analysis of venlafaxine by Thase and colleagues[45] was company sponsored.

Cognitive therapy (CT) has been shown to benefit patients who have only a partial remission with antidepressant treatment.[46] Patients randomized to continue pharmacotherapy with the addition of CT had significantly reduced relapse rates compared with those who continued pharmacotherapy alone (29% v. 47%). In a long-term prospective study, patients receiving continuation therapy with a modified version of CT designed to address residual symptoms after antidepressant treatment had a significantly lower level of residual symptoms and a lower rate of relapse over 6 years of

follow-up.[24,32,34] Similar results were reported in patients with recurrent depression, where those receiving continuation therapy with CT had a significantly lower level of residual symptoms, and at the 2-year follow-up had a much lower rate of relapse (25%) than the clinical management group (80%).[47]

Results from acute combination treatment with both pharmacotherapy and psychotherapy for depression have been inconsistent.[48] However, a study by Keller and colleagues[49] suggests that, in addition to increasing overall response rates, combination treatment with nefazodone and the cognitive behavioral analysis system of psychotherapy significantly increases rates of complete remission (HAM-D < 8) compared with drug therapy or psychotherapy alone.[49]

Summary

Despite the inconsistencies in the research concerning partial remission — the definition being first and foremost — it is clear that residual depressive symptoms are associated with a range of clinically significant negative outcomes. Even patients with minimal levels of residual symptoms are at greater risk of early relapse into depression. They are burdened with greater levels of social dysfunction and experience higher rates of physical morbidity and mortality than patients who have achieved full remission. Residual symptoms may relate, in part, to an incompatibility between the treatment and the patient (personality factors) — further research is needed to allow a better prediction of the best match. It is clear that treatment strategies should be directed toward reducing residual symptoms.

Competing interests: None declared for Dr. O'Donovan. Dr. Tranter received an honorarium for participating in the development and writing of this article and travel assistance to attend a symposium and meetings related to this article from Wyeth-Ayerst. Dr. Chandarana has received honoraria, travel assistance and speaker's fees from Wyeth-Ayerst, GlaxoSmithKline and Eli Lilly. Dr. Kennedy has received research support from Pfizer, Astra-Zeneca, Organon and Boehringer Ingelheim; is on the speakers' bureaus of Lundbeck, Organon, Wyeth-Ayerst and GlaxoSmithKline; and serves on advisory boards for Pfizer, the Lundbeck Foundation, Eli Lilly, GlaxoSmithKline and Servier.

References

1. Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, et al. Lifetime and 12-month prevalence of DSM III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. *Arch Gen Psychiatry* 1994;51:8-19.
2. Broadhead WE, Blazer DG, George LK, Tse LK. Depression, disability days and days lost from work in a prospective epidemiologic survey. *JAMA* 1990;264:2524-8.
3. Sherbourne CD, Wells KB, Hays RD, Rogers W, Burnam MA, Judd LL. Subthreshold depression and depressive disorder: clinical characteristics of general medicine and mental health specialty outpatients. *Am J Psychiatry* 1994;151:1777-84.
4. Murray CJL, Lopez AD. *The global burden of disease and global health statistics*. Boston (MA): Harvard University Press; 1996.
5. Paykel ES, Ramana R, Cooper Z, Hayhurst H, Kerr J, Barocka A. Residual symptoms after partial remission: an important outcome in depression. *Psychol Med* 1995;25:1171-80.
6. Keller MB, Shapiro RW, Lavorin PW, Wolfe N. Relapse in major depressive disorder: analysis with the life table and regression models. *Arch Gen Psychiatry* 1982;39:911-15.
7. Rush A, Trivedi M. Treating depression to remission. *Psychiatr Ann* 1995;25:704-10.
8. Katon W, Lin E, Von Korff M, Bush T, Walker E, Simon G, et al. The predictors of persistence of depression in primary care. *J Affect Disord* 1994;31:81-90.
9. Coryell W, Endicott J, Keller M. Outcomes of patients with chronic affective disorder: a five-year follow-up. *Am J Psychiatry* 1990;147:1627-33.
10. Frank E, Prien RF, Jarrett RB, Keller MB, Kupfer DJ, Lavori PW, et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. *Arch Gen Psychiatry* 1991;48:851-5.
11. Simon GE. Long-term prognosis of depression in primary care. *Bull World Health Organ* 2000;78:439-45.
12. Thase ME, Simmons AP, McGeary J, Cahalane JF, Hughes C, Harden T, et al. Relapse after cognitive behavior therapy of depression: potential implications for longer courses of treatment. *Am J Psychiatry* 1992;149:1046-52.
13. Nierenberg AA, Keefe BR, Leslie VC, Alpert JE, Pava JA, Worthington JJ 3rd, et al. Residual symptoms in depressed patients who respond acutely to fluoxetine. *J Clin Psychiatry* 1999;60:221-5.
14. Opdyke KS, Reynolds CF, Frank E, Begley AE, Buysse DJ, Dew MA, et al. Effect of continuation treatment on residual symptoms in late-life depression: how well is "well"? *Depress Anxiety* 1996/97;4:312-19.
15. Ezquiaga E, Garcia A, Bravo F, Pallares T. Factors associated with outcome in major depression: a 6-month prospective study. *Soc Psychiatry Psychiatr Epidemiol* 1998;33:552-7.
16. Judd LL, Rapaport MH, Paulus MP, Brown JL. Subsyndromal symptomatic depression (SSD): a new mood disorder? *J Clin Psychiatry* 1994;55:18S-28S.
17. Judd LL, Akiskal HS, Paulus MP. The role and clinical significance of subsyndromal depressive symptoms (SSD) in unipolar major depression. *J Affect Disord* 1997;167:6-10.
18. Lin EH, Katon WJ, Simon GE, Von Korff M, Bush TM, Walker EA, et al. Low-intensity treatment of depression in primary

care: is it problematic. *Gen Hosp Psychiatry* 2000;22:78-83.

19. Weissman MM, Prusoff RA, Klemen GL. Personality in the prediction of long-term outcomes of depression. *Am J Psychiatry* 1978;135:797-800.

20. Ormel J, Oldehinkel T, Brilman E, van den Brink W. Outcome of depression and anxiety in primary care: A three-wave 3 1/2 year study of psychopathology and disability. *Arch Gen Psychiatry* 1993;50:759-66.

21. Brodaty H, Harris L, Peters K, Wilhelm K, Hickie I, Boyce P, et al. Prognosis of depression in the elderly: a comparison with younger patients. *Br J Psychiatry* 1993:163:589-96.

22. Judd LL, Akiskal HS, Maser JD, Zeller PJ, Endicott J, Coryell W, et al. Major depressive disorder: A prospective study of residual subthreshold depressive symptoms as predictor of rapid relapse. *J Affect Disord* 1998;50:97-108.

23. Kupfer DJ, Spiker DG. Refractory depression: prediction of non-response by clinical indicators. *J Clin Psychiatry* 1981;42: 307-12.

24. Fava GA, Grandi S, Zielezny M, Canestrati R. Cognitive-behavioral treatment of residual symptoms in primary major depressive disorder. *Am J Psychiatry* 1994;15:1295-99.

25. Pava J, Nierenberg A, Carey M, et al. Residual symptoms in major depression: a comparison with normal controls. Presented at the 147th Annual Meeting of the American Psychiatric Association; 1994 May 22–26; Philadelphia (PA).

26. Bagby RM, Joffe RT, Parker JDA, Kalembra V, Harkness KL. Major depression and the five-factor model of personality. *J Pers Disord* 1995;9:224-34.

27. Shea T, Leon A, Mueller T, Solomon DA, Warshaw MG, Keller MB. Does major depression result in lasting personality change? *Am J Psychiatry* 1996;153:1404-10.

28. Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. A longitudinal twin study of personality and major depression in women. *Arch Gen Psychiatry* 1993;50:853-62.

29. Hirschfeld RM, Russell JM, Delgado PL, Fawcett J, Friedman RA, Harrison WM, et al. Predictors of response to acute treatment of chronic and double depression with sertraline or imipramine. *J Clin Psychiatry* 1998;59:669-75.

30. Ramana R, Paykel ES, Cooper Z, Hayhurst H, Saxty M, Surtees PG. Remission and relapse in major depression: a two-year prospective follow-up study. *Psychol Med* 1995;25:1161-70.

31. Faravelli C, Ambonetti A, Palente S, Pazzagli A. Depressive relapse and incomplete recovery from index episode. *Am J Psychiatry* 1986;143:888-91.

32. Fava GA, Grandhi S, Zielezny M, Canestrati R. Four-year outcome for cognitive behavioral treatment of residual symptoms in major depression. *Am J Psychiatry* 1996;153:945-7.

33. Simmons AD, Thase ME. Biological markers, treatment outcome, and 1-year follow-up in endogenous depression: electroencephalographic sleep studies and response to cognitive therapy. *J Consul Clin Psychol* 1992;60:392-401.

34. Fava G, Silvana G, Zielezny M, Canestrari R, Morphy MA. Six-year outcome for cognitive behavioral treatment of residual symptoms primary major depressive disorder. *Am J Psychiatry* 1998;155:1443-5.

35. Georgotas A, McCue RE, Cooper TB, Hagachandran N, Chang I. How effective and safe is continuation therapy in elderly depressed patients: factors affecting relapse rate. *Arch Gen Psychiatry* 1988;929-32.

36. Evans MD, Hollon SD, De Rubeis RJ, Piasecki JM, Grove WM, Garvey MJ, et al. Differential relapse following cognitive therapy and pharmacotherapy for depression. *Arch Gen Psychiatry* 1992;49:802-8.

37. Judd LL, Paulus MJ, Schettler PJ, Akiskal HS, Endicott J, Leon AC, et al. Does incomplete recovery from first lifetime major depressive episode herald a chronic course of illness? *Am J Psychiatry* 2000;157:1501-4.

38. Frasure-Smith N, Lesperance F, Talajic M. Depression and 18-month prognosis and myocardial infarction. *Circulation* 1995; 91:999-1005.

39. Frasure-Smith N, Lesperance F, Juneau M, Talajic M, Bourassa MG. Gender, depression, and one-year prognosis after myocardial infarction. *Psychosom Med* 1999;61:26-37.

40. Lesperance F, Frasure-Smith N, Juneau M, Theroux P. Depression and 1-year prognosis in unstable angina. *Arch Intern Med* 2000;160:1354-60.

41. Horsten M, Mittleman MA, Wamala SP, Schenck-Gustafsson K, Orth-Gomer K. Depressive symptoms and lack of social integration in relation to prognosis of CHD in middle-aged women. The Stockholm Female Coronary Risk Study. *Eur Heart J* 2000;21:1072-80.

42. Jonas BS, Mussolino ME. Symptoms of depression as a prospective risk factor for stroke. *Psychosom Med* 2000;62:463-71.

43. Barbui C, Hotopf M. Amitriptyline v. the rest: still the leading antidepressant after 40 years of randomised controlled trials. *Br J Psychiatry* 2001;178:129-44.

44. Anderson IM. Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. *J Affect Disord* 2000;58:19-36.

45. Thase M, Entsuah AR, Rudoph, RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br J Psychiatry* 2001;178:234-41.

46. Paykel ES, Scott J, Teasdale JD, Johnson AL, Garland A, Moore R, et al. Prevention of relapse in residual depression by cognitive therapy. *Arch Gen Psychiatry* 1999;56:829–35.

47. Fava GA, Rafanelli C, Grandi S, Conti S, Belluardo P. Prevention of recurrent depression with cognitive behavioural therapy. *Arch Gen Psychiatry* 1998;55:816–20.

48. Conte HR, Plutchik R, Wild KV, Karasu TB. Combined psychotherapy and pharmacotherapy for depression: a systematic analysis of the evidence. *Arch Gen Psychiatry* 1986;43:471-9.

49. Keller MB, McCullough JP, Klein DN, Arnow B, Dunner DL, Gelenberg AJ, et al. A comparison of nefazodone, the cognitive-behavioural analysis system of psychotherapy, and their combination for the treatment of chronic depression. *N Engl J Med* 2000;342:1462-70.