

Major Depression in 1998: Are We Providing Optimal Therapy?

Jules Angst, M.D.

Depression is a common illness associated with long duration of episodes, high rates of chronicity, relapse and recurrence, psychosocial and physical impairment, and high suicide rate. A lifetime prevalence of approximately 17% has been widely reported, and the likelihood of recurrence is more than 50%. A conceptual shift has occurred in our understanding of depression. It is now seen as a chronic medical disorder that produces as much functional limitation and morbidity as chronic diseases such as hypertension and diabetes. Predictors of chronicity include long duration of index episode, relationship difficulties, low family income, admitting research center, and inpatient hospitalization. Risk factors for recurrence include lack of self-confidence, neuroticism, previous hospital admission, loss events, and age. The aim of treatment is to induce a stable, fully asymptomatic state with full restoration of psychosocial function and to establish a long-term state of wellness. Despite effective pharmacotherapy, depressed patients are often underdiagnosed and undertreated by both psychiatrists and primary care physicians. The psychosocial and physical impairment, comorbidity, and high suicide rate associated with chronic, recurrent depression require optimal treatment strategies. The future of antidepressant treatment should focus on remission or getting the patient well and drugs that will induce and maintain long-term recovery.

(J Clin Psychiatry 1999;60[suppl 6]:5-9)

Depression is a pernicious illness associated with long duration of episodes, high rates of chronicity, relapse and recurrence, as well as psychosocial and physical impairment.¹ Disabilities caused by depression can occur in both social and work roles and can impact both familial well-being and economic status.¹ It should be remembered that depression is seen in the health care setting as often as common medical conditions such as diabetes or chronic lung disease. A lifetime prevalence of depression of between 17% and 19% was reported by the National Comorbidity Survey, which was the first study to administer a structured psychiatric interview to a national probability sample in the United States.² These findings confirm the high rates found in Switzerland^{3,4} and are in contrast to the results of the U.S. Epidemiologic Catchment Area (ECA) study.⁵ Recently, the Depression Research in European Society (DEPRES) study, which investigated depression in 6 European countries and in over 80,000 subjects, found that 17% of subjects had some form of depression over a 6-month period,⁶ which is consistent with findings in other countries.²

The message from epidemiologic data is that a need exists for increased recognition and treatment of patients with major depressive disorders. Further, once diagnosed, there is a need for effective long-term treatment of depression. Finally, there is a need for pharmacologic treatment that provides more than just improvement in symptoms but offers the best opportunity for complete remission and for prevention of relapse and recurrence.

DEPRESSION: A CONCEPTUAL SHIFT

Epidemiologic data from a number of countries demonstrate that major depression is a chronic, recurrent condition. Between 15% and 20% of patients have symptoms that persist for at least 2 years, and often these patients do not fully recover between depressive episodes.⁷ Epidemiologic studies indicate that the likelihood an individual who has suffered one episode of depression will experience a second episode is probably greater than 40%.⁸⁻¹⁰ Furthermore, when a patient experiences a second episode of depression, the probability that he or she will develop a third episode is increased.⁹

These high rates of relapse and recurrence are troubling since depression is associated with a substantial risk of mortality, including up to a 15% risk of death from suicide in patients with more severe forms of the disease.¹¹⁻¹⁴ Indeed, in the United States, patients with major depression account for about half of all suicides, and 15% of patients hospitalized for major depression commit suicide.¹⁵

Although poorly recognized, clinical depression causes greater impairment of physical and social functioning than

From the Department of Psychiatry, Research Department, Psychiatric University Hospital, Zurich, Switzerland.

Presented at the satellite symposium "Goal of Antidepressant Therapy: Response or Remission and Recovery?" which was held at the 21st Collegium Internationale Neuropsychopharmacologicum Congress, July 14, 1998, in Glasgow, Scotland, and supported by an unrestricted educational grant from Wyeth-Ayerst Laboratories.

Reprint requests to: Jules Angst, M.D., Research Department, Psychiatric University Hospital, P.O. Box 68, Lengstrasse 31, CH-8029 Zurich, Switzerland.

many other chronic medical illnesses such as hypertension, diabetes, or arthritis.¹⁶ With these findings, an important conceptual shift has occurred in our understanding of depression, where depression represents a chronic and recurrent disease that often requires maintenance treatment.

COURSE AND OUTCOME OF DEPRESSION

Research over the past decades has documented that the course and outcome of depression are much less favorable than frequently assumed.¹⁷ The overall goals of treatment for major depression are the attainment of a stable, fully asymptomatic state and full restoration of psychosocial function.¹⁸ Thus, with effective treatment, patients should progress from response to remission and recovery, but these positive outcomes may be interrupted with periods of relapse and recurrence.¹⁹ A number of factors have been identified that predict a chronic outcome or an increased risk of relapse or recurrence of major depression.

Predictors of Chronic Outcome

A number of comparable long-term follow-up studies have documented the poor outcome from major depression.^{11–14,17,20} During follow-up periods of 10 to 20 years or more, up to 62% of patients were rehospitalized for depression, 11% to 34% experienced a poor outcome, and suicide was common (Table 1). Several variables have been identified as predictors of a chronic outcome from major depression in the first 2 years of follow-up. These include long duration of index episode before intake, marital status, relationship difficulties, low family income, admitting research center, and a history of nonaffective psychiatric disorders.^{6,21} Other predictors of longer time to recovery are secondary unipolar subtype, inpatient hospitalization at entry, and secondary or comorbid illness such as anxiety disorders or alcohol/substance abuse.⁶ Additional sociodemographic variables found to predict a lower recovery rate include older age and female gender.²²

Of these variables, long duration of index episode is still the best predictor of time to recovery.⁶ Indeed, examination of probabilities of recovery clearly demonstrates that the longer a patient is ill, the lower the current rate of recovery (Figure 1).^{23,24} In a study by Keller and colleagues,²³ approximately half of subjects with major depression recovered within the first 6 months; however, the yearly rate of recovery subsequently declined markedly during a follow-up to 10 years. For patients still depressed, the likelihood of recovery within the next month declined by 1% to 2% per month during years 3, 4, and 5 of follow-up.

Predictors of Recurrence

Once unipolar depression develops, it has a very high probability of becoming recurrent (Figure 1). Lavori and associates⁹ reported that 13% of patients experience a recurrence 6 months after recovery from an index episode of

Table 1. Outcome From Long-Term Follow-Up Studies of Patients With Major Depression

Reference	Number of Patients	Follow-Up (y)	% of Patients		
			Readmitted	Poor Outcome	Suicide
Lee and Murray ¹⁴	89	18	62	28	10 ^a
Kiloh et al ¹³	133	15	56	11	7
Thornicroft and Sartorius ¹²	439 ^b	10	35	18	11
Surtees and Barkley ²⁰	80 ^c	12	40	34	8
Angst and Preisig ¹¹	186	22–27	...	13	13

^aIncludes probable suicide/suspect unnatural deaths.

^b62.8% inpatients.

^c87.5% inpatients.

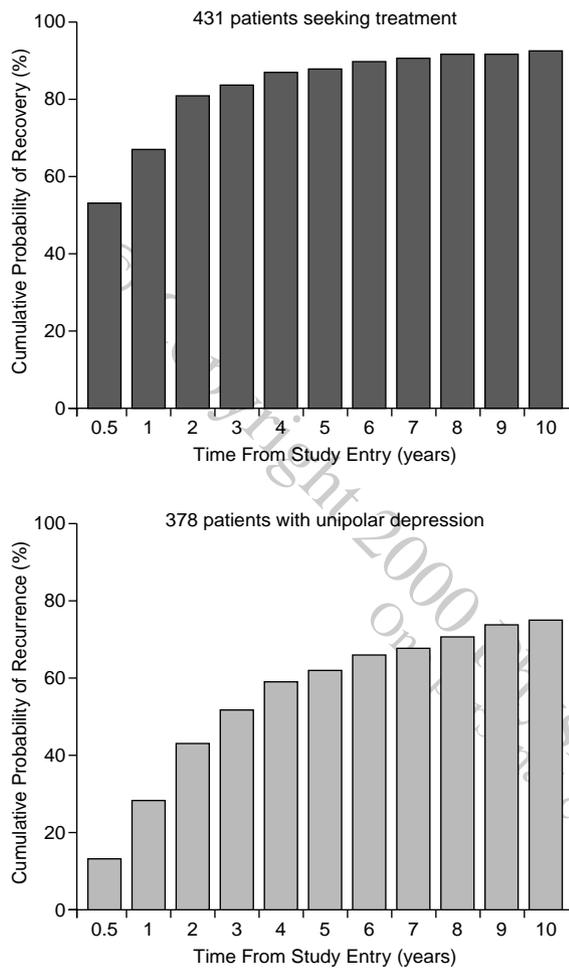
depression. However, the cumulative probability of recurrence more than doubles at 1 year and triples at 2 years after recovery. According to this study, three quarters of patients experienced a recurrence 5 years after recovery from an index episode of depression, confirming earlier European follow-up studies of Angst and Preisig.¹¹

Although the cumulative probability of recurrence increases over time, a number of variables have some prognostic value for recurrence. A study by Surtees and Wainwright²⁵ showed that relationships between psychosocial, clinical, and demographic factors and long-term outcome indicate that psychosocial factors, in particular neuroticism and a lack of self-confidence, have the greatest prognostic significance. Indeed, limited self-confidence is strongly related to the subsequent first recurrence of affective disorder. An episode of loss events and previous hospital admission are also considered risk factors for recurrence. These results reveal the heightened risk over the long term of a poor outcome for depressive disorder consequent upon measures of personality deviance and of exposure to adversity.²⁵ Additional risk factors for recurrence include a history of frequent and/or multiple episodes of depression, “double depression” (i.e., major depression plus preexisting dysthymia), onset after age 60, and a long duration of individual episodes.^{23,26,27} In contrast, the diagnosis of “melancholic” features or the severity of the depressive episode has no significant effect on the recurrence of depression.

A study by Paykel et al.²⁸ demonstrated that the presence of residual symptoms after partial remission impacts on the outcome of depression. Residual depression, which has been characterized as a Hamilton Rating Scale for Depression (HAM-D) score above 8, has been reported in one third of patients with major depression. Residual symptoms occur more frequently in patients with more severe illness and include anxiety, negative thought content (e.g., guilt and hopelessness), impairment of activities, anorexia, and early insomnia. The presence of residual symptoms may be a strong predictor of relapse or recurrence of depression.

Clearly, the presence of residual depression symptoms increases the risks of relapse/recurrence of depression, but

Figure 1. Recovery (top) and Recurrence After Recovery (bottom) From an Index Episode of Major Depression^a



^aAdapted from references 23 and 24, with permission.

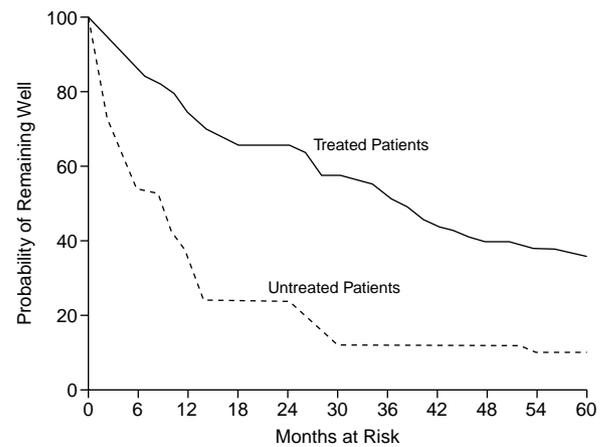
also could be associated with an increased risk of comorbid psychiatric conditions such as anxiety disorder. This evidence of the impact of residual symptoms on patient outcomes highlights the need for antidepressant treatment that produces full recovery and remission.

UNDERTREATMENT OF DEPRESSION

The mortality and morbidity associated with depression emphasize the importance of identifying and adequately treating this disorder.²⁹ However, despite compelling evidence that effective treatment is available, patients with depression are underdiagnosed and undertreated by both psychiatrists and primary care physicians.^{1,27}

Results from studies conducted in Europe and the United States clearly indicate that patients with depression consistently receive no or subtherapeutic doses of antidepressant therapy.³⁰ For example, an analysis of 250 patients admitted to a major medical center for the treatment of depression revealed that as many as 31% had been

Figure 2. Differences in Outcome Between Treated and Untreated Patients With Major Depression^a



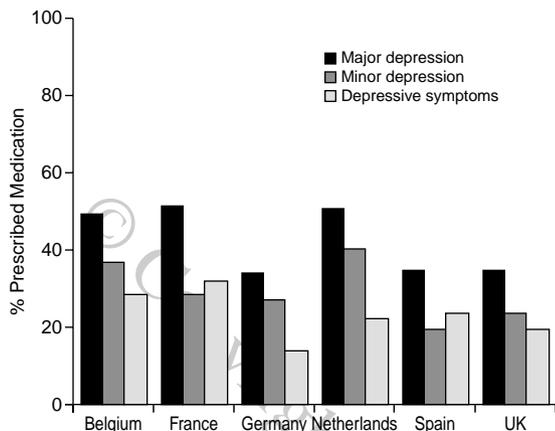
^aAdapted from reference 32, with permission.

given no or very low amounts of antidepressant during the first 8 weeks of care.³⁰ A study of 20 patients who were chronically depressed for 2 years demonstrated that half had not been treated or received minimal treatment.⁶ In another study, 47% of patients who were experiencing a recurrent episode of depression did not receive any preventative treatment in the month prior to the next depressive episode.³¹ The inadequacy of treatment of recurrent depression was confirmed in another investigation, which showed that more than 50% of patients with recurrent depression in whom a chronic depressive disorder developed and persisted for at least 1 year were given subtherapeutic doses of medication or none at all.²⁶

These findings are especially disturbing given the difference in outcome between treated and untreated patients. Maj and colleagues³² followed the course of depression over 5 years in treated and untreated patients with major depression and found a significantly *lower* probability of remaining well in those patients who remained untreated (Figure 2). Further, the undertreatment of depression appears to be a widespread phenomenon in Western countries. An early finding of the European DEPRES study, comprising more than 80,000 subjects, was that one third of subjects with major depression had not consulted a health care professional about their depression.⁶ Importantly, among the 69% of patients with depression or symptoms of depression who had consulted a health care professional, 41% had been prescribed drug therapy, but only 18% had received an antidepressant (Figure 3). The data cited in the DEPRES study are surprisingly low and tend to confirm the conclusion that depression is being undertreated.⁶

Even when depression is treated, the duration of treatment may be inadequate. A prospective, population-based study conducted in Scotland found that both tricyclic anti-

Figure 3. Proportion of Depressed Patients Treated With Medication in European Countries From the DEPRES (Depression Research in European Society) Study^a



^aAdapted from reference 6, with permission.

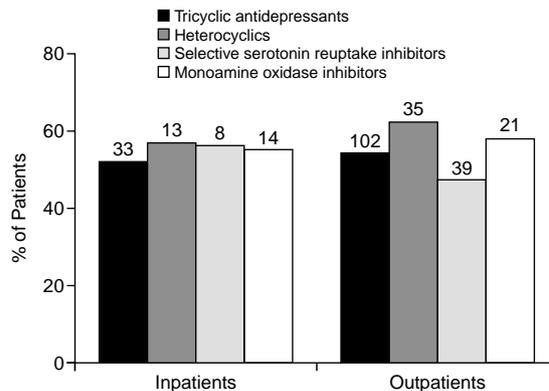
depressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) were given for an inadequate duration, and almost three quarters of patients received subtherapeutic doses of TCAs.³³ Altogether, these data suggest that there is a large burden of untreated or undertreated depression.

PHARMACOTHERAPY OF DEPRESSION

Inadequate levels of antidepressant treatment have been rationalized on the basis of inadequate diagnosis, poor patient compliance, and concerns over side effects and potential overdose attempts. In addition, the preference of some clinicians for psychosocial treatments or other somatic treatments may contribute to inadequate pharmacotherapy. However, effective treatment requires continued pharmacologic management for most individuals with recurrent depression.¹⁹

Indeed, provided they are given at adequate dosages for an adequate duration, antidepressants are effective treatments for depression.³³ However, a meta-analysis of randomized, controlled trials reported that about half of inpatients receiving TCAs, SSRIs, monoamine oxidase inhibitors (MAOIs), or heterocyclics responded to treatment, as measured by at least a 50% reduction in HAM-D score (Figure 4).¹⁸ Similarly, approximately 50% to 60% of outpatients with major depression responded to therapy with one of these agents.¹⁸ Thus, the data suggest that the majority of depressed patients who complete a short-term course of antidepressant therapy show improvement in symptoms of depression, although not always full recovery. Although there is some evidence of differential efficacy between antidepressant classes, there is little evidence of differential efficacy between members of the same class.

Figure 4. Meta-Analysis of Response Rate (= 50% reduction in HAM-D or MADRS) From Controlled Trials of Patients With Major Depressive Disorder^a



^aFrom reference 18. Abbreviations: HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale.

However, the 50% to 60% initial response to treatment fails to address the 10% to 20% of patients who cannot tolerate antidepressant therapy at an adequate dosage or the 25% to 35% of patients who do not respond to available antidepressants. Also, data on response rates fail to consider the need to induce remission and long-term recovery. Results from short- and long-term studies suggest a treatment goal to be lower rates of remission and long-term recovery.⁹

CONCLUSION

Depression is one of the most common medical illnesses and a serious cause of disability to patients.^{1,16} As such, it is a major public health problem that is often underrecognized and undertreated. However, the realization that major depression is often both chronic and recurrent has slowly begun to change the way that this disorder is diagnosed and treated. Increasingly, the need for long-term continuation and maintenance treatment is recognized.

Nonetheless, the psychosocial and physical impairment, comorbidity, and high suicide rate associated with chronic and recurrent depression indicate a need for continued progress in developing optimal treatment strategies. Ideally, these strategies should induce full remission, maintain long-term recovery, and be effective in treating depression and comorbid disorders. The future direction of antidepressant treatment should focus on remission, or getting the patient well.

REFERENCES

1. Hirschfeld RMA, Keller MB, Panico S, et al. The National Depressive and Manic-Depressive Association consensus statement on the undertreatment of depression. *JAMA* 1997;277:333-340

2. Kessler RC, McGonagle KA, Zhao 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
3. Angst J. The prevalence of depression. In: Briley M, Montgomery SA, eds. *Antidepressant Therapy at the Dawn of the Third Millennium*. London, England: Martin Dunitz; 1998:191–212
4. Wacker HR, Müllejahns R, Klein KH, et al. Identification of cases of anxiety disorders and affective disorders in the community according to ICD.10 and DSM-III-R by using the Composite International Diagnostic Interview (CIDI). *Int J Methods Psychiatr Res* 1992;2:91–100
5. Weissman MM, Bruce LM, Leaf PJ, et al. Affective disorders. In: Robins LN, Regier DA, eds. *Psychiatric Disorders in America: The Epidemiologic Catchment Area Study*. New York, NY: The Free Press; 1991:53–80
6. Lepine JP for the DEPRES Steering Committee. European perspective on depression. *Prim Care Psychiatry* 1997;3(suppl 1):S3–S6
7. Keller MB, Klerman GL, Lavori PW, et al. Long-term outcome of episodes of major depression: clinical and public health significance. *JAMA* 1984; 252:788–792
8. Angst J, Baastrup P, Grof P, et al. The course of monopolar depression and bipolar psychoses. *Psychiatr Neurol Neurochir* 1973;76:489–500
9. Lavori PW, Keller MB, Mueller TI, et al. Recurrence after recovery in unipolar MDD: an observational follow-up study of clinical predictors and somatic treatment as a mediating factor. *Int J Methods Psychiatr Res* 1994;4: 211–229
10. Van Londen L, Molenaar RPG, Goekoop JG, et al. Three- to 5-year prospective follow-up of outcome of major depression. *Psychol Med* 1998;28: 731–735
11. Angst J, Preisig M. Outcome of a clinical cohort of unipolar, bipolar and schizoaffective patients: results of a prospective study from 1959 to 1985. *Schweiz Arch Neurol Psychiatr* 1995;146:17–23
12. Thornicroft G, Sartorius N. The course and outcome of depression in different cultures: 10-year follow-up of the WHO Collaborative Study on the Assessment of Depressive Disorders. *Psychol Med* 1993;23:1023–1032
13. Kiloh LG, Andrews G, Neilson M. The long-term outcome of depressive illness. *Br J Psychiatry* 1988;153:752–757
14. Lee AS, Murray RM. The long-term outcome of Maudsley depressives. *Br J Psychiatry* 1988;153:741–751
15. Kapur S, Mieczkowski T, Mann JJ. Antidepressant medications and the relative risk of suicide attempt and suicide. *JAMA* 1992;268:3441–3445
16. Wells KB, Stewart A, Hays RD, et al. The functioning and well-being of depressed patients: results from the Medical Outcomes Study. *JAMA* 1989; 262:914–919
17. Angst J. Clinical course of affective disorders. In: Helgason T, Daly RJ, eds. *Depressive Illness: Prediction of Course and Outcome*. New York, NY: Springer; 1988:1–48
18. Clinical Practice Guideline Number 5: Depression in Primary Care, vol 2. *Treatment of Major Depression*. Rockville, Md: US Dept Health Human Services, Agency for Health Care Policy and Research; 1993. AHCPR publication 93-0551
19. Kupfer DJ. Long-term treatment of depression. *J Clin Psychiatry* 1991;52 (5, suppl):28–34
20. Surtees PG, Barkley C. Future imperfect: the long-term outcome of depression. *Br J Psychiatry* 1994;164:327–341
21. Keller MB, Klerman GL, Lavori PW, et al. Treatment received by depressed patients. *JAMA* 1982;248:1848–1855
22. Maj M. Predictors of course of depression. *Curr Opin Psychiatry* 1994;7: 22–25
23. Keller MB, Lavori PW, Mueller TI, et al. Time to recovery, chronicity, and levels of psychopathology in major depression: a 5-year prospective follow-up of 431 subjects. *Arch Gen Psychiatry* 1992;49:809–816
24. Keller MB. Depression: considerations for treatment of a recurrent and chronic disorder. *J Psychopharmacol* 1996;10(suppl 1):41–44
25. Surtees PG, Wainwright NW. Fragile states of mind: neuroticism, vulnerability and the long-term outcome of depression. *Br J Psychiatry* 1996;169: 338–347
26. Keller MB, Lavori PW, Rice J, et al. The persistent risk of chronicity in recurrent episodes of nonbipolar major depressive disorder: a prospective follow-up. *Am J Psychiatry* 1986;143:24–28
27. Keller MB. Depression: underrecognition and undertreatment by psychiatrists and other health care professionals. *Arch Intern Med* 1990;150: 946–948
28. Paykel ES, Ramana R, Cooper Z, et al. Residual symptoms after partial remission: an important outcome in depression. *Psychol Med* 1995;25: 1171–1180
29. Keller MB. Depression: a long-term illness. *Br J Psychiatry* 1994;165 (suppl 26):9–15
30. Keller MB, Lavori PW, Klerman GL, et al. Low levels and lack of predictors of somatotherapy and psychotherapy received by depressed patients. *Arch Gen Psychiatry* 1986;43:458–466
31. Keller MB, Lavori PW, Lewis CE, et al. Predictors of relapse in major depressive disorder. *JAMA* 1983;250:3299–3304
32. Maj M, Veltro F, Pirozzi R, et al. Pattern of recurrence of illness after recovery from an episode of major depression: a prospective study. *Am J Psychiatry* 1992;149:795–800
33. MacDonald TM. Treatment of depression: prescription for success? *Prim Care Psychiatry* 1997;3(suppl 1):S7–S10