British Journal of Psychiatry (1994), **165** (suppl. 26), 9–15

Depression: A Long-Term Illness

MARTIN B. KELLER

The realisation that major depression is often both chronic and recurrent has slowly begun to change the way that depression is diagnosed and treated. In particular, the need for continuation and maintenance treatment is an issue that now deserves increased attention, especially with the availability of new classes of antidepressant treatments, which have excellent efficacy and more favourable side-effect profiles. Although the serious consequences of depressive disorders clearly indicate the need for effective and prompt intervention on the part of clinicians, the results of several studies indicate that patients with depression consistently receive no or low levels of antidepressant therapy. It is hoped that, through continued education of health care providers and patients about the consequences of depression, the issue of undertreatment of this serious illness will be resolved.

Until recently, depression was thought of as a psychiatric disorder in which discrete episodes of illness alternated with clearly defined 'well periods' during which patients returned to their previous state of health (Kraepelin, 1921).

For more than a decade, research and clinical observation have shown that patients with depression have a significant likelihood of experiencing relapse, recurrence, chronicity, and residual 'subsyndromal' symptoms between full-criteria episodes of illness (Regier *et al*, 1988*a*). In addition, depression is one of the most common psychiatric illnesses; data gathered by the Epidemiological Catchment Area study indicate an 8% lifetime prevalence for depression in the general population (Regier *et al*, 1988*a*). Death from suicide is markedly increased among depressed individuals, and approaches an incidence of 15% for hospitalised patients with depression (Kandel & Davies, 1986; Berglund & Nilsoson, 1987; Murphy *et al*, 1987; Perugi *et al*, 1988). It is therefore important for health care providers to be aware that major depression may become a chronic and/or recurrent disorder. Furthermore, treatment should be continued not only in those patients suffering from this disorder even when symptoms have abated to subsyndromal levels, but also in those patients who have fully recovered from the episode of depression.

Time to recovery

Since its inception in 1974, the United States National Institute of Mental Health (NIMH) Collaborative Study of the Psychobiology of Depression (CDS) has consistently provided evidence that depression is a chronic and recurrent condition. The ongoing CDS is a 19-year, longitudinal prospective study of 965 patients with a mood disorder and 3500 of their first-degree relatives, thereby affording investigators a unique opportunity to observe the course of depression. Depressed probands were evaluated at six-month intervals for five years, and thereafter at annual intervals for at least 10 years (Keller *et al*, 1992). At each point in time, data suggest that a significant proportion of patients remained chronically ill, despite the previous, widely-held belief that depressed patients tend to recover (as defined by a return to the pre-depression state) from acute depressive episodes.

In 1984, for example, after a two-year study of 97 patients with major depressive disorder, 21% of the subjects had not recovered (Keller *et al*, 1984). Given that the median duration of illness before enrolment in the study was approximately one year among the non-recovered subjects, these data suggest that a significant portion of the subjects were chronically ill for three years. Factors that were found to predict a prolonged time to recovery were longer duration and increased severity of the index episode, history of a non-affective psychiatric disorder (suggesting secondary depression), lower family income, and marital status (married) during the index episode (Keller *et al*, 1984). In addition, after five years, the majority of patients who did not recover experienced subsyndromal symptoms of depression; their illness resembled chronic minor depression or dysthymia with episodes of major depression, rather than major depression alone (Keller *et al*, 1992).

The cumulative probability of recovery for 431 CDS subjects who entered the study in an episode of major depression, with no history of mania,

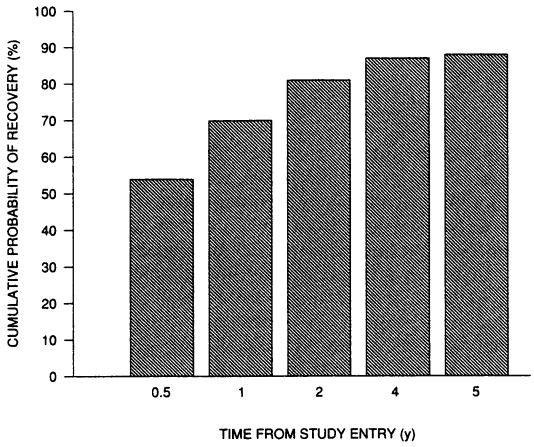

Fig. 1 Cumulative probability of recovery from the index episode of major depression for 555 patients with unipolar depression evaluated for five years (Keller *et al*, 1992).

Table 1
Predictors of chronicity or relapse in patients with major depression (Keller *et al*, 1982, 1983*a*, 1986*a*)

Chronicity	Relapse
Long duration of index episode before treatment	History of three or more episodes
RDC secondary unipolar subtype	If first episode of depression: (a) secondary depression
In-patient hospitalisation	(b) increased age
Low family income	
Intact marriage	

RDC = Research Diagnostic Criteria.

hypomania, schizoaffective disorder, underlying minor depression, or chronic intermittent depression (defined as dysthymia in DSM–III and DSM–III–R), was 88% after five years of prospective follow-up (Keller *et al*, 1992). Probabilities were calculated for intervals ranging from one week to five years, and showed that the chances of recovery from major depression were highest within the first six months following entry into the study (Fig. 1). The longer the duration of illness, the less likely recovery became. Only 18% of the patients still suffering from depression after one year recovered between years 1 and 5, whereas 54% recovered during the first six months after enrolment in the study.

Six factors were found to be significantly associated with a chronic course of depression: a long episode duration before entry into the study; the admitting research centre; marital status (married); in-patient hospitalisation status at intake; low family income; and the presence of Research Diagnostic Criteria (RDC) for secondary-unipolar subtypes (i.e. schizophrenia, panic, obsessive–compulsive, phobia, schizoaffective disorder, drug addiction, alcoholism, anorexia, and organic brain syndrome) (Table 1) (Keller *et al*, 1984). Based on the 21% rate of chronicity following one year of follow-up, it was determined that a long prior episode, older age, and low family income were predictive of chronicity in the first prospective episode (Keller *et al*, 1986*a*). Furthermore, a non-significant trend towards slower recovery was found in patients who were divorced or separated, versus those who were married or single (Keller *et al*, 1986*a*).

In addition to those patients who continued to suffer from depression, approximately 25% of the patients who recovered during the first year of follow-up relapsed within 12 weeks of recovery (Keller *et al*, 1986*a*). Of those, nearly half relapsed during the first four weeks after recovering. In particular, those subjects with underlying chronic depression had a significantly greater chance of relapse into an episode of major depression during the first month following recovery than patients who had major depression only (30% v. 4%, $P<0.01$). After one year, the rate of recurrence among patients with underlying chronic depression was 33% (Lavori *et al*, 1993).

A number of other researchers have investigated the frequency of recurrence and chronicity in major depression (Akiskal *et al*, 1980; Rounsaville *et al*, 1980; Angst, 1988). Their data confirm that a significant number of depressed patients experience multiple episodes and/or lengthy episodes without a return to the 'pre-depression' state of well-being. Angst, for example, followed patients with depression for 20 years and found that 15% to 20% of patients developed a chronic course of illness and that up to 20% committed suicide (Angst, 1988). Additionally, he determined that these patients spent as much as 20% of their lifetime in depressive episodes. In the Zurich study of depression conducted by Angst, a cohort of individuals were evaluated for ten years to trace the epidemiology and course of the disorder (Angst, 1992). Over the course of a single year, about 30% of the depressions were "monophasic", and over ten years, only 25% of patients had a single episode. These data suggest that the majority of patients with depression (75–80%) experience multiple episodes. Furthermore,

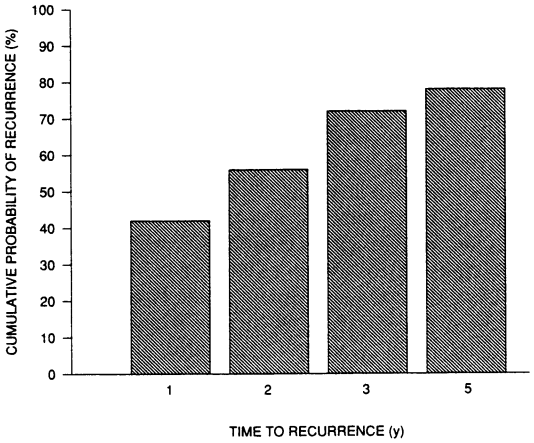

Fig. 2 Cumulative probability of recurrence after recovery from the index episode of major depression in 555 patients with unipolar depression evaluated for five years (Lavori *et al*, 1993).

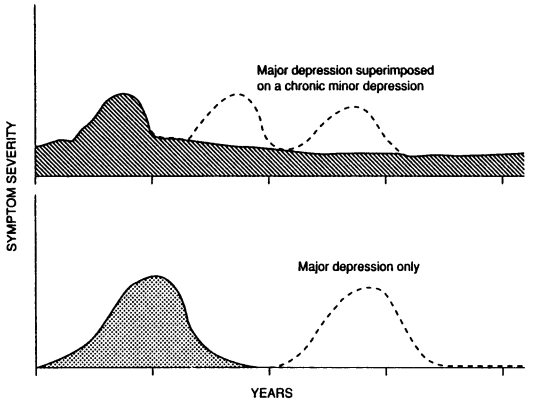

Fig. 3 Schematic of symptom severity in patients with double depression (top) or major depression alone (bottom).

sociodemographic variables such as race, social class, education level, marital status, religion, intelligence, gender, age, positive family history of depression, and growing up in a 'broken home' did not predict outcome in depressive episodes.

Relapse and recurrence

Among patients who do recover from acute episodes of major depression, relapse is frequent, although the risk of relapse tends to decrease the longer the patient remains well. In a study of 141 depressed collaborative subjects who recovered from the index episode of illness, the cumulative probability of relapse was 22% after one year of follow-up (Keller *et al*, 1983*a*). Patients who had previously had three or more episodes of major depression had shorter times from recovery to relapse than other patients. For patients with their first episode of depression, a greater age and a history of a previous non-affective psychiatric illness predicted a significantly shorter time to relapse (Table 1).

In a further analysis of 359 patients with unipolar depression, in which treatment as an intervening variable for recurrence risk was assessed, the results strongly suggested that continuing a high level of somatotherapy in the first few months after the start of remission is associated with a better chance of remaining well (Lavori *et al*, 1993). The analysis also suggested that the prognostic significance of continued somatotherapy is greatest at the start of remission.

According to the most recent analysis, the predicted median length of the 'well' interval is about 20 months (2 months of 'required' remission and 18 months at risk), with only 60% of patients achieving one year of well-being (Lavori *et al*, 1993). The probability of sustaining a recovery for as long as five years is only 22% (Fig. 2). Several factors predict an increased risk of recurrence, including duration of episode, prior number of episodes, and secondary or endogenous subtypes of depression. Among subjects who did not have underlying chronic depression, the number of previous episodes of major depression was found to predict time to relapse. Subjects who had had three or more previous episodes had a 43% chance of relapse by the 12th week following recovery, whereas those with fewer than three previous episodes had an 11% chance of relapse over the same time period ($P = 0.026$).

Double depression

Another factor that strongly influences the course of depression is the presence of 'double depression'. This phenomenon has been defined as the concurrent presence of both dysthymia and major depressive disorder, in which acute major depressive episodes appear to be superimposed on the underlying chronic depression (Fig. 3) (Keller & Shapiro, 1982). The presence of double depression implies that patients recovering from acute major depressive episodes rarely return to a pre-illness state of well-being. Dysthymia is, by definition, chronic; DSM–III–R criteria for the disorder require depressed mood that is present for at least two years, although with less severe symptoms than those of major depressive disorder (American Psychiatric Association, 1987).

Prior to the CDS investigations of double depression, Rounsaville *et al* (1980) reported that only 34% of 64 patients with depression met the criteria for major depression alone. The remainder suffered from some form of chronic minor depression, such as intermittent depressive disorder (36%), cyclothymic personality (15%), and labile personality (16%). Similarly, Akiskal *et al* (1980) reported that 55% of patients with depression presented with "chronic characterological depression" and superimposed major depressive disorder.

In addition to these earlier reports, an analysis of the first 101 depressed patients enrolled in the CDS revealed that 26% of patients had an underlying chronic depression of at least a two-year duration (Keller & Shapiro, 1982). In 20 of those patients, the underlying minor depression met the criteria for dysthymia.

After a one-year follow-up period, patients with double depression were more likely to have recovered from their acute episode of major depressive disorder than patients with major depressive disorder alone (88% v. 69%), although this was not significant (Keller & Shapiro, 1982). However, the majority of these patients (58%) did not recover from their underlying, chronic minor depression. An analysis of the length of chronic depression before entry into the study indicates that 96% of the patients with double depression had chronic minor depression lasting three years or more; 73% had been ill for five years or longer, and 42% had been ill for ten years or more. In addition, patients with double depression had a significantly ($P<0.01$) higher rate of relapse into an episode of major depression than patients with major depression alone.

In a subsequent two-year follow-up study of 316 CDS patients, 80 patients with 'double depression' were identified (Keller *et al*, 1983*b*). After two years, 97% of patients with double depression (versus 79% of the patients with major depression alone) had recovered from the index episode of major depression. However, 58% had still not recovered from the underlying dysthymia. This longer study period allowed a more in-depth examination of the course, predictors of course, and sociodemographic features of patients with double depression. Three variables predicted a shorter time to recovery in all doubly depressed patients: a shorter duration of the index episode of depression; more acute onset of the index episode; and less severe Hamilton Depression Rating Scale scores. Patients with double depression had shorter yet more severe episodes of major depression and were, again, more likely to relapse than patients with major depression alone (Keller *et al*, 1983*b*).

Once again, the time to recovery from the index episode of major depression was shorter in double-depressed patients. Among those still ill at one year, there was an 82% probability of recovery during the second year, compared with only 29% for patients with major depression alone. Although the patients with double depression recovered from acute major depression at a median of 13 weeks from entry, recovery from chronic minor depression had not been observed in approximately 60% of patients after 104 weeks of follow-up (Keller *et al*, 1983*b*).

When the course of illness of the two groups was followed for six months, it was found that more patients with double depression than major depression alone failed to recover (75% v. 32%) (Klein *et al*, 1988). In addition, 29% of patients with double depression developed RDC definite or probable hypomania during the follow-up period, as opposed to 9% of the patients with episodic major depression. Overall, patients with double depression reported higher mean levels of depression and poorer global functioning, as measured by the Beck Depression Inventory and the Social Adjustment Scale (Klein *et al*, 1988).

These data suggest that double depression is relatively common among patients with major depression, and that the presence of underlying chronic minor depression has clinical and prognostic significance. Patients with double depression recover from major depressive episodes quickly, but their recovery from chronic minor depression is slow. Those who do recover from the major depressive episode tend to relapse more frequently and rapidly. In addition, the longer these patients remain chronically ill, the more likely they are to relapse. Therefore, clinicians treating patients with double depression should institute intensive somatotherapy to prevent the development of a chronic illness.

Undertreatment of depression

As noted previously, the CDS is a naturalistic study. No attempt was made to control the type or duration of treatment received by the subjects. However, information on treatment received was gathered. Although it is not possible to infer a causal link between the treatment data and the high rate of chronicity, relapse, and recurrence found in our sample, it is clinically important to note that most of the CDS subjects received inadequate treatment for their depressive episodes, both before and after they were enrolled in the study (Table 2).

Treatment data were gathered on the first 217 depressed subjects entering the CDS, and focused on the treatment that the patients received in the

Table 2
Treatment during the index episode of unipolar major depression before and after entry into the CDS (Keller *et al*, 1982, 1986*b*)

Treatment	% before entry ($n=217$)	% after entry (in-patients) ($n=250$)	% after entry (out-patients) ($n=88$)
TCA/MAOI, 4-week maximum level			
none	66	22	30
$\geqslant$250 mg/d[1]	3	45[2]	27[2]
Neuroleptics	26	19	3
Minor tranquilizers	55	36	24
Psychotherapy	67	81	48

MAOI = monoamine oxidase inhibitor; TCA = tricyclic antidepressant.
1. Dosage of antidepressant was corrected to imipramine equivalents.
2. Percentage of patients is based on dosage of $\geqslant$200 mg/d.

community setting, before enrolling in the study. Most subjects received psychotherapy (67%) or anti-anxiety medications (55%: Keller *et al*, 1982). Only 34% of patients received antidepressant medication for four consecutive weeks, and only 3% received the most intensive possible dose. Of the patients who did receive antidepressants, most received the equivalent of 150 mg of imipramine for only one month. Similarly low levels of treatment during the first eight weeks of the study period were found in a subsequent evaluation of 338 CDS patients (Keller *et al*, 1986*b*). Additionally, after two and five years of evaluation, 31% to 50% of patients received no or low levels of antidepressant treatment (Keller *et al*, 1986*b*; Keller, 1990). Among those who recovered and then relapsed, 47% were found to have had no antidepressant treatment in the four weeks prior to relapse (Keller *et al*, 1983*a*).

In addition to these CDS findings reflecting the undertreatment of depression, several other research groups have published similar data (Frank *et al*, 1989; Kupfer *et al*, 1989; Thase, 1990; Levitt *et al*, 1991; Maj *et al*, 1992). Some researchers have concentrated on whether early intervention shortens the length of an episode and others have focused on assessing the prospective pattern of recurrence following short-term treatment and recovery. There is concurrence among investigators that prophylactic drug treatment can reduce the risk of recurrence, and that the relatively low use of proven, available treatments by clinicians who recognised major depression in their patients is puzzling. Socio-demographic and clinical variables were of very limited value in predicting which patients were likely to receive adequate treatment. Although it is not possible to conclude that all patients with major depression receive inadequate treatment, it is clear that the reasons for undertreatment need further scrutiny.

Likewise, it is not possible to conclude that a causal link exists between low treatment levels and the strong evidence of chronicity and relapse in depressed patients. However, research data demonstrate a tendency for patients receiving the lowest levels of somatotherapy to remain ill for the longest period of time (Keller *et al*, 1986*b*). This suggests that some severely depressed patients who have been labelled "treatment resistant" may, in fact, have received inadequate treatment and for too short a time (Keller, 1988). Given the high levels of morbidity and mortality associated with depression, it is especially disturbing that this illness remains underdiagnosed and undertreated (Keller, 1990).

Towards DSM-IV

Our understanding of depression continues to evolve and expand. In preparation for the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV: American Psychiatric Association, 1994), a Mood Disorders Field Trial Task Force was developed by the American Psychiatric Association (APA) to assess the relationship between major depression, dysthymia, minor depression, and depressive personality disorder. The Field Trial was designed to address some of the problems with the DSM-III-R mood disorders section. For example, the severity and course criteria for major depression and depressive personality disorder are not clear, and in the clinical samples used, more than 80% of the subjects with dysthymia also meet the criteria for major depression (American Psychiatric Association, 1987).

The preliminary findings from the Field Trial have had a significant impact on redefining the depressive disorders for DSM-IV. Moreover, substantial changes will be made in the definition of dysthymic disorders to differentiate them more clearly from major

depression. For example, in DSM-III-R, the defining symptoms of dysthymia do not include many of the cognitive and affective symptoms thought to be most characteristic of the disorder. The criteria place emphasis on vegetative and psychomotor symptoms that, based on the Field Trial data, are more applicable to major depression and will be weighted more heavily in the new criteria for major depression. In addition, other criteria, including age of onset, are being considered, based on data found.

Members of the Mood Disorders Task Force of the APA have agreed that course modifiers are necessary to provide a more complete and accurate clinical picture of depression. Because understanding the course is essential to the treatment of an illness, it is important to document and understand various patterns that the illness may take. For example, all patients with major depression will be classified as suffering from a single episode or recurrent depression, and the frequency and temporal relationship of episodes of dysthymia and major depression will be described.

Conclusions

The serious consequences of depressive disorders indicate the need for swift and effective intervention on the part of psychiatrists, and of other physicians who may encounter patients with depression in their medical practices. Unfortunately, the results of studies that have focused on the amount and type of treatment received by these patients consistently reflect the opposite. Patients with depression often receive no or low levels of antidepressant treatment and psychotherapy. Factors such as the severity of the symptoms and length of the depressive illness appear to influence the treatment received.

Given the complexity of the treatment decision problem, no single report, to date, fully explains the reason for the gap between the availability of treatments demonstrated by controlled clinical trials to be effective for depression, and the treatment actually received by individual patients in clinical practice. Several issues seem to contribute, including the failure to diagnose depression accurately, patients' lack of compliance, or preference of the clinicians to use strictly psychosocial therapy. Clinicians are also concerned about the side-effects of antidepressants and about the potential for overdose or misuse of these medications.

To address these problems, the US NIMH launched the Depression Awareness, Recognition, and Treatment (DART) Program in 1988. This programme, which includes objectives targeted to the public and to health care providers, was designed to alert audiences to the prevalence and seriousness of depressive disorders and to the availability of treatment (Regier *et al*, 1988*b*). It is imperative that clinicians who treat depressed patients remain aware of the insidious nature of the illness and of the many effective options available for its treatment.

Acknowledgement

The author would like to thank Liz Prager for her outstanding organisation, editing and referencing of this material. Her invaluable assistance is deeply appreciated.

References

AKISKAL, H. S., ROSENTHAL, T. L., HAYKAL, R. F., *et al* (1980) Characterological depressions: clinical and sleep EEG findings separating "subaffective dysthymias" from "character spectrum disorders". *Archives of General Psychiatry*, **37**, 777–783.

AMERICAN PSYCHIATRIC ASSOCIATION (1987) *Diagnostic and Statistical Manual of Mental Disorders* (3rd edn, revised) (DSM-III-R). Washington, DC: APA.

——— (1994) *Diagnostic and Statistical Manual of Mental Disorders* (4th edn) (DSM-IV). Washington, DC: APA.

ANGST, J. (1988) Clinical course of affective disorders. In *Depressive Illness: Prediction of Course and Outcome* (eds T. Helgson & R. J. Daly). Berlin: Springer.

——— (1992) How recurrent and predictable is depressive illness? In *Long-Term Treatment of Depression* (eds S. Montgomery & F. Rouillon). New York: John Wiley.

BERGLUND, M. & NILSOSON, K. (1987) Mortality in severe depression: a prospective study including 103 suicides. *Acta Psychiatrica Scandinavica*, **76**, 372–380.

FRANK, E., KUPFER, D. J. & PEREL, J. M. (1989) Early recurrence in unipolar depression. *Archives of General Psychiatry*, **46**, 397–400.

KANDEL, D. & DAVIES, M. (1986) Adult sequelae of adolescent depressive symptoms. *Archives of General Psychiatry*, **43**, 255–262.

KELLER, M. B. (1988) Undertreatment of major depression. *Psychopharmacology Bulletin*, **24**, 75–80.

——— (1990) Depression: underrecognition and undertreatment by psychiatrists and other health care professionals. *Archives of Internal Medicine*, **150**, 946–948.

———, KLERMAN, G. L., LAVORI, P. W., *et al* (1982) Treatment received by depressed patients. *Journal of the American Medical Association*, **248**, 1848–1855.

——— & SHAPIRO, R. W. (1982) "Double depression": superimposition of acute depressive episodes on chronic depressive disorders. *American Journal of Psychiatry*, **139**, 438–442.

———, LAVORI, P. W., LEWIS, C. E., *et al* (1983*a*) Predictors of relapse in major depressive disorder. *Journal of the American Medical Association*, **250**, 3299–3304.

———, ———, ENDICOTT, J., *et al* (1983*b*) "Double depression": two-year follow-up. *American Journal of Psychiatry*, **140**, 689–694.

———, KLERMAN, G. L., LAVORI, P. W., *et al* (1984) Long-term outcome of episodes of major depression: clinical and public health significance. *Journal of the American Medical Association*, **252**, 788–792.

———, LAVORI, P. W., RICE, J., *et al* (1986*a*) The persistent risk of chronicity in recurrent episodes of nonbipolar major depressive disorder: a prospective follow-up. *American Journal of Psychiatry*, **143**, 24–28.

———, ———, KLERMAN, G. L., *et al* (1986*b*) Low levels and lack of predictors of somatotherapy and psychotherapy received by depressed patients. *Archives of General Psychiatry*, **43**, 458–466.

———, ———, MUELLER, T. I., *et al* (1992) Time to recovery, chronicity, and levels of psychopathology in major depression: a five-year prospective follow-up of 431 subjects. *Archives of General Psychiatry*, **49**, 809–816.

KLEIN, D. N., TAYLOR, E. B., HARDING, K., *et al* (1988) Double depression and episodic major depression: demographic, clinical, familial, personality, and socioenvironmental characteristics and short-term outcome. *American Journal of Psychiatry*, **145**, 1226–1231.

KRAEPELIN, E. (1921) *Manic Depressive Insanity and Paranoia* (ed. G. M. Robertson, trans. R. M. Barclay). Edinburgh: Livingstone.

KUPFER, D. J., FRANK, E. & PEREL, J. M. (1989) The advantage of early treatment intervention in recurrent depression. *Archives of General Psychiatry*, **46**, 771–775.

LAVORI, P. W., KELLER, M. B., SCHEFTNER, W., *et al* (1994) Recurrence after recovery in unipolar MDD: an observational follow-up study of clinical predictors and somatic treatment as a mediating factor. *International Journal of Methods in Psychiatric Research* (in press).

LEVITT, A. J., JOFFE, R. T. & MACDONALD, C. (1991) Life course of depressive illness and characteristics of current episode in patients with double depression. *Journal of Nervous and Mental Disease*, **179**, 678–682.

MAJ, M., VELTRO, F., PIROZZI, R., *et al* (1992) Pattern of recurrence of illness after recovery from an episode of major depression: a prospective study. *American Journal of Psychiatry*, **149**, 795–800.

MURPHY, J., MONSON, R., OLIVIER, D. C., *et al* (1987) Affective disorders and mortality. *Archives of General Psychiatry*, **44**, 473–480.

PERUGI, G., MAREMMANI, I., MCNAIR, D., *et al* (1988) Differential changes in areas of social adjustment from depressive episodes through recovery. *Journal of Affective Disorders*, **15**, 39–43.

REGIER, D. A., BOYD, J. H., BURKE, J. D., Jr, *et al* (1988*a*) One-month prevalence of mental disorders in the United States: based on five epidemiologic catchment area sites. *Archives of General Psychiatry*, **45**, 977–986.

———, HIRSCHFELD, R. M. A., GOODWIN, F. K., *et al* (1988*b*) The NIMH Depression Awareness, Recognition, and Treatment Program: structure, aims, and scientific basis. *American Journal of Psychiatry*, **145**, 1351–1357.

ROUNSAVILLE, B. J., SHOLOMSKAS, D. & PRUSOFF, B. A. (1980) Chronic mood disorders in depressed outpatients: diagnosis and response to pharmacotherapy. *Journal of Affective Disorders*, **2**, 73–88.

THASE, M. E. (1990) Relapse and recurrence in unipolar major depression: short-term and long-term approaches. *Journal of Clinical Psychiatry*, **51** (suppl. 6), 51–57.

Martin B. Keller, MD, Psychiatrist-in-Chief, Butler Hospital, and Executive Psychiatrist-in-Chief, Brown Affiliated Hospitals, 345 Blackstone Boulevard, Providence, RI 02906, USA