THE COURSE OF DEPRESSION

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Long-term naturalistic studies have changed the way we view depression. Whereas it was often previously viewed as an episodic disease, the past two decades of research have underscored the importance of understanding depression as a lifelong disease, with a number of possible courses.

An appreciation of this longitudinal data is crucial to understanding all aspects of depression. Cross-sectional judgments of symptomatic severity provide limited prognostic information. A full understanding of a patient's prognosis or likely treatment response also requires a longitudinal perspective. Which patient is likely to recover fully, and who will suffer from a chronic mood disorder? What length of treatment will be sufficient for such patients?

Studies within the last decade have helped to shed light on these questions. This chapter examines some of these studies, and discusses their implications for our approach to depression. Limitations of the data will be discussed as well.

THE CHANGE POINTS OF DEPRESSION

Considerable confusion has resulted from the use of various terms to denote the different change points in the course of depression. Similar terms, such as "relapse" and "recurrence" have been used interchangeably and inconsistently in different studies. As a result, the MacArthur Foundations Research Network on the Psychobiology of Depression (1) recommended using the following terms:

- 1. *Episode*, defined as a certain number of symptoms for a certain period of time.
- 2. *Remission*, defined as a period of time in which an individual no longer meets criteria for the disorder. In partial
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- remission, an individual still has more than minimal symptoms. Full remission is defined as the point at which an individual no longer meets criteria for the disorder and has no more than minimal symptoms.
- 3. *Recovery*, defined as a full remission that lasts for a defined period of time. Conceptually, it implies the end of an episode of an illness, not of the illness per se.
- 4. *Relapse*, defined as a return of symptoms sufficient to satisfy full criteria for an episode. It occurs in an interval of time before what is defined as "recovery." Conceptually, this refers to the return of an episode, not a new episode.
- Recurrence, defined as a return of full symptomatology occurring after the beginning of the recovery period. Conceptually, this represents the beginning of a new episode of an illness.

REPRESENTATIVE STUDIES

A relatively small number of studies have been particularly influential in shedding light on the course of depression.

The Collaborative Depression Study (CDS)

The CDS (2) is a prospective long-term naturalistic study of the natural course of depression. Subjects were recruited from patients with depression seeking psychiatric treatment at one of several sites (university or teaching hospitals in Boston, Chicago, Iowa City, New York, and St. Louis). This study included programs in biological and clinical studies. The data presented here are from the clinical studies program; 555 subjects in the clinical studies program had an index episode of unipolar major depression. Subjects were examined at 6-month intervals for 5 years and then annually for a minimum of 18 years. Recent National Institute of Mental Health (NIMH) funding will extend the follow-up to at least 23 years on all subjects.

The Zurich Study

Angst (3), in Zurich, has conducted the only other long-term prospective study of mood disorders. In that study, 173 hospitalized patients with unipolar depression were identified between 1959 and 1963. This group was then evaluated every 5 years for up to 21 years of follow-up.

The Medical Outcomes Study (MOS)

The MOS (4) examined the course of several diseases (myocardial infarction, congestive heart failure, hypertension, diabetes, and depression) in a variety of health care settings, including large medical group practices, small group practices, and solo practices, in three cities (Los Angeles, Boston, and Chicago). A representative sample of different medical specialties—including psychiatry—was chosen, and all patients seen from February through October 1986 were asked to participate in the study. In all, over 20,000 patients participated, and were evaluated yearly for 3 years.

THE COURSE OF DEPRESSION: CHANGE POINTS

Traditionally, depression was pictured as an acute illness, self-limited, and lasting approximately 6 to 9 months from time of onset to full recovery. A number of studies, including those mentioned above, however, show the potential for great variation from this traditional model. Recovery may take much longer, or not occur at all (i.e., chronic depression). Furthermore, the risk of relapse and recurrence of illness must be considered.

Recovery

In the CDS, approximately 70% of patients recovered from the index episode of major depression within the first year (5). However, for those patients who did not recover in the first year, most still had not recovered within 5 years. Thus by 2 years, about 20% of the original sample were still depressed—two-thirds of those still depressed at 1 year were still in their index episode of depression at 2 years. At 5 years, 12% of patients had still not recovered (6), by 10 years 7% had not recovered (7), and by 15 years, the numbers seem to have leveled off at 6%. These data are presented in Fig. 69.1.

The long duration of the CDS allowed the investigators to observe subsequent episodes of major depression beginning during the study. This was particularly useful, as the onset of symptoms could be identified more accurately than for the retrospective determination done for an index episode. It was found that, for each new episode of depression, the rates of recovery were similar to that seen during the index episode. Thus, for the second episode (first prospectively observed episode) approximately 8% of subjects did not recover after 5 years. An analysis of subsequent episodes (second, third, and fourth prospectively observed episodes) showed similar findings. By the fifth episode, the rate decreases, but not significantly so (8). It appears that for each episode of depression, some individuals—about 10%—remain ill for at least 5 years.

The seemingly high rate of chronicity was surprising. A reasonable concern about this result was that the patient population studied may have been unusually treatment resistant. The study used a convenient sample of patients seeking inpatient or outpatient treatment at any one of five major medical centers. However, most patients studied received either no treatment or subtherapeutic doses given for very brief durations (9). Thus, the CDS cohort does not seem to be biased in the direction of treatment resistance.

Furthermore, other studies show comparable data. In the Zurich study, Angst et al. (10) reported that during the

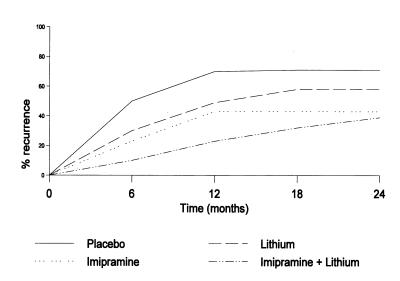


FIGURE 69.1. Outcome of maintenance therapy for depressed patients initially stabilized on imipramine plus lithium.

follow-up evaluations, about 13% of patients did not recover from their episode of major depression. In the MOS, patients were divided by severity: of those with milder depression, about 65% recovered within 2 years, whereas 54% of the more severely depressed group recovered in the same period (11).

Shorter studies also give similar results. Rounsaville and colleagues (12), in a prospective follow-up of 96 patients with major depression, found that 12% of subjects had not recovered after 16 months. Kerr et al. (13), following initially hospitalized patients, found that 6% remained ill for the 4 years of the study.

Relapse

For the 141 patients in the CDS who recovered from their index episode of major depression, 22% relapsed within 1 year of follow-up (14). Factors predicting relapse included multiple episodes of major depression, older age, and a history of nonaffective psychiatric illness. The characteristics of this relapsed group were also examined, and it was found that the likelihood of remaining depressed for at least a year after relapse was 22%. Predictors of prolonged time to recovery included a longer length of the index episode, older age, and a lower family income.

Most studies look at relapse in terms of how it is affected by treatment (see below).

Recurrence

Angst (15), reporting on a 10-follow of patients in the Zurich study, found that only 25% of patients had only a single episode of depression. Thus, three-fourths of the sample had a recurrent depression, with one or more recurrences. Though Angst examined a number of sociodemographic variables, none significantly predicted the likelihood of recurrence.

Similarly high rates of recurrence have been found in other long-term studies. Weissman and Kasl (16) found that two-thirds of woman seen over 1 year had a recurrence of depression. Rao and Nammalvar (17), examining over 100 cases of depression in India for a follow-up of between 3 and 13 years, found that only about a fourth of the original group reported no recurrence of symptoms.

The rate and timing of recurrence seems most dependent on the type of recovery. Patients in the CDS who fully recovered (i.e., were asymptomatic on follow-up evaluation) had a much lower rate of recurrence (66%) than those with some residual symptoms (87%). The time to recurrence was also much longer in the asymptomatic group: mean of 180 weeks in the asymptomatic group compared with 33 weeks in the group with residual symptoms (18).

MITIGATING FACTORS

Comorbidity

Medical Illness

There are few longitudinal studies looking at the outcome of depression in medically ill patients, partly because of the difficulties inherent in recruiting such an unstable population. Studies that exist suggest that comorbid medical illness predispose individuals to a worse course of depression. The MOS, for example, found an additive effect on patient functioning when depression and other chronic medical illnesses were combined (19).

Double Depression

Double depression refers to the presence of concurrent dysthymia and major depression. In this disorder, the episodes of major depression are superimposed on a more chronic depressive disorder. It appears to be common—studies suggest that between one-fourth and two-thirds of patients with major depression will also have a comorbid dysthymia.

The comorbid presence of dysthymia can have an important effect on the course of depression. In the collaborative study, it was found that patients with double depression recovered more rapidly from episodes of major depression than those with major depression alone. However, the authors also found that the recovery tended to be not to one of "normalcy," but to one of dysthymia. Relapse is also more frequent in patients with double depression than those with major depression alone—almost twice as likely in one study of 32 double-depressed subjects followed for 2 years (20). The MOS also found that full recovery was less likely for patients with double depression—these patients had a threefold risk of continued disease when compared with those with major depression alone (21).

Other Psychiatric Illnesses

Substance Abuse

Clearly, comorbid substance abuse has a detrimental effect on the course of depression. The CDS found that subjects who were currently alcoholic were half as likely as nonalcoholic depressed subjects to recover from their episode of major depression (22). Patients with a previous, but not current, history of alcoholism had a recovery rate comparable to those with no such history.

Anxiety Disorders

Anxiety disorders are commonly comorbid with depression. The presence of such comorbid disorders appears to exert a negative effect on the course of depression. Coryell and colleagues (23) found that depressed patients with panic disorder had a slower time to recovery than those without

comorbid panic. The CDS similarly found that patients with higher symptom ratings of anxiety had longer times to recovery from major depression (24).

Family History

A family history of depression appears to predispose an individual to depression. Two studies have looked at the relationship between parental history of depression and course of depression in the offspring. Though these studies had relatively small sample sizes, they both suggested that patients with a parental history of depression had a longer time to recovery than other patients (25,26).

Treatment Variables

Clearly, one of the questions of most practical interest is whether pharmacologic treatment is capable of significantly altering the course of depression for a patient. Antidepressants are generally used at all stages of depression—to hasten recovery, prevent relapse, and prevent recurrence of depression. However, as will be discussed, the further one looks down the course of depression, the less is really known about the ability of antidepressant and other pharmacologic treatments to alter the course of depression.

A wealth of data supports the efficacy of all available antidepressants in shortening the time to recovery from major depression. However, when one goes beyond the acute phase and examines pharmacotherapy during later points in the course of depression, the data become more meager.

Data support the efficacy of most of the serotonin reup-

TABLE 69.1. RELAPSE RATES VS. PLACEBO: CONTINUATION STUDIES

Drug (Reference)	Weeks of Treatment	Relapse (Drug) %	Relapse (Placebo) %	P Value
Fluoxetine (27)	52	26	57	<.01
Paroxetine (28)	52	16	43	<.001
Sertraline (29)	44	13	46	<.001
Citalopram (30)	24	11	31	<.05
Nefazodone (32)	36	17	33	<.05
Mirtazapine (31)	20	4	23	<.0001

take inhibitors for continuation therapy, including fluoxetine (27), paroxetine (28), sertraline (29), citalopram (30), and mirtazapine (31). Nefazodone has also been shown in continuation treatment (32). These studies are summarized in Table 69.1. However, when looking beyond continuation therapy to the maintenance treatment of recurrent depression, much fewer data exist.

Prien and colleagues (33) reported on a 2-year maintenance trial for depression. Patients who were successfully treated for acute depression were randomized to receive lithium carbonate, imipramine, both, or placebo. Treatments were continued for 2 years with doses maintained at acute treatment levels. Of 150 patients beginning maintenance treatment, 36% were successfully treated. The lowers rate of recurrence was found it the group treated with imipramine (Fig. 69.1). However, even this group had a 47% recurrent rate.

A second study, the Pittsburgh Study of Maintenance Treatment for Recurrent Depression (34), reports on up to

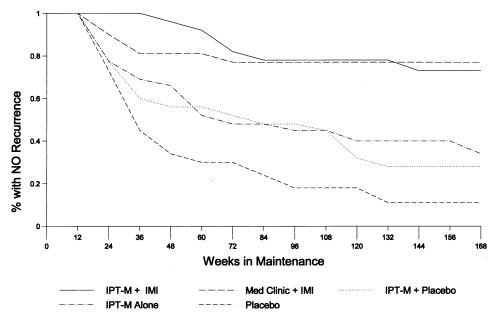


FIGURE 69.2. Pittsburgh Study of Maintenance Therapies in Recurrent Depression.

5 years of maintenance treatment. In this study, subjects first underwent open treatment for acute depression, using imipramine with interpersonal therapy (IPT). Patients who achieved recovery for at least 4 months were then randomized into one of five treatment conditions: (a) IPT alone, given monthly; (b) imipramine treatment alone; (c) IPT plus placebo; (d) placebo plus medication clinic; and (e) imipramine plus IPT. This portion of the study was continued for 3 years. Results from this study are summarized in Fig. 69.2.

The authors intentionally chose patients who had highly recurrent depression (to maximize the likelihood of seeing a statistical difference in the groups). They found that patients who received imipramine (with or without IPT) had an approximately 20% risk of recurrence after 3 years. This compares significantly with the other conditions: IPT alone had a 60% risk of recurrence, and the placebo condition had an 80% risk.

This study was extended, with a smaller sample, for another 2 years. The subjects who had remained well during the first 3 years of the study were randomized to receive either imipramine or placebo. At that point only 20 patients remained in the study. After the two additional years, less than 10% of the patients (one patient out of 11) receiving imipramine had a recurrence, where approximately two-thirds of the placebo group had a recurrence.

Thus, the world literature of placebo-controlled studies of the treatment of recurrent depression beyond 3 years consists of only 200 subjects, who had a history of highly recurrent depression and received a medication that is rarely used by most psychiatrists today.

OTHER SUBTYPES OF DEPRESSION

The data are also limited when one considers the effect of treatment on the course of specific subtypes of depression. Two such subtypes will be considered here: chronic major depression and dysthymia.

Treatment Of Chronic Depression

Chronic depression is thought to respond more poorly to antidepressant treatment. Thus, studies of the acute and long-term treatment for this subtype are of great importance. Particularly lacking are studies of psychotherapy in this population.

Keller and colleagues (35) recently compared antidepressant treatment and cognitive-behavioral therapy, both alone and combined. For the 519 subjects completing the study, 55% of the antidepressant (nefazodone) group and 52% of the psychotherapy group responded to treatment. However, when treatment was combined, the response rate jumped to 85%. Thus, this study gives strong support to the clinical wisdom that combined treatment is preferable to either medication or psychotherapy alone.

To date, there are only two published studies on the long-term treatment of chronic depression. Kocsis and colleagues (36) report on a placebo-controlled trial of desipramine for the treatment of chronic depression. The study included patients with chronic major depression (n = 14).

After successful acute-phase and continuation treatment, patients were continued on treatment for a total of 2 years. During this maintenance period, patients on the placebo had four times the recurrence rate of those receiving desipramine. This rate was consistent for all diagnostic groups, including those with chronic depression.

Keller and colleagues (37) investigated the treatment of chronic depression in a larger sample of patients. Here, 161 patients who were successfully treated during an acute-phase and continuation phase were randomized to receive with sertraline or placebo for a 76-week maintenance period. The study included both chronic major depression and double depression patients in roughly equal numbers; as the results did not differ between the groups, the data was pooled.

Patients who received the placebo during the maintenance phase of treatment were four times more likely to have a recurrence of depression than those receiving sertraline. The time to recurrence was delayed for patients treated with sertraline compared to those treated with the placebo. Using a less stringent criterion of reemergence of depressive symptoms (though no necessarily meeting full criteria for depression), it was found that only 26% of patients taking sertraline experienced a reemergence of depressive symptoms, compared with 50% of those on the placebo. Similarly, only 34% of patients on sertraline maintenance therapy shored first symptoms of depression, compared with 60% of patients taking the placebo (Table 69.2).

TABLE 69.2. RECURRENCE RATES OF MAJOR DEPRESSION DURING MAINTENANCE STUDY TREATMENT

	Sertraline (n = 77)	Placebo (<i>n</i> = 84)	P Value
Suffered recurrence by strict protocol criteria (%)	6	23	.002
Suffered depression reemergence by consensus assessment (%)	26	50	.001
Showed first symptoms of reemergence of depression by consensus assessment (%)	34	60	.001

From Keller MB, Kocsis JH, Thase ME, et al. Maintenance phase efficacy of sertraline for chronic depression: a randomized controlled trial. *JAMA* 1998;280:1665–1672, with permission.

TABLE 69.3. PHARMACOTHERAPY OF DYSTHYMIA: SELECTED AGENTS
DEMONSTRATING A POSITIVE EFFECT IN RANDOMIZED-CONTROLLED
TRIALS

Drug	Compared to:	Study	Duration of Study (Weeks)	
Imipramine	Placebo	Koesis et al., 1985 (38)	6	
	Phenelzine, placebo	Stewart et al., 1993 (39)	6	
Desipramine	Placebo	Stewart et al., 1983 (40)	6	
Fluoxetine	Placebo	Hellerstein et al., 1993 (41); Vanelle, 1997 (42)	8; 12	
Sertraline	Placebo	Ravindran et al., 1994 (43)	12	
	Imipramine, placebo	Thase et al., 1996 (44)	12	
	Imipramine	Keller et al., 1995 (45)	12	
Ritanserin	Imipramine, placebo	Bakish et al., 1994 (46)	7	
Moclobemide	Placebo	Botte et al., 1992 (47)	4	
	Imipramine, placebo	Versiani et al., 1997 (48)	8	
Amisulpride	Amineptine, placebo	Boyer and Lecrubier, 1996 (49)	12	
	Fluoxetine	Smeraldi, 1998 (50)	12	

Treatment Of Dysthymia

Few studies have examined the pharmacotherapy of dysthymia, possible because of long-held beliefs that nonmajor depressions were less responsive to pharmacotherapy. What data do exist, however, do not support this belief. Most studies are of a relatively short duration of treatment, ranging from 4 to 12 weeks. For this time period there are data to support the use of most classes of antidepressants. These studies are summarized in Table 69.3. Thus, the weight of evidence suggests that most agents that are effective for major depression are also effective for dysthymia, at least in the acute phase of treatment.

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