The Naturalistic Course of Unipolar Major Depression in the Absence of Somatic Therapy

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Abstract: The goal of the study was to describe the naturalistic course of unipolar major depression in subjects not receiving somatic therapy for their depressive illness. Affectively ill individuals were recruited into the Collaborative Depression Study and followed prospectively for up to 15 years. One hundred thirty subjects who recovered from their intake episode of major depression subsequently experienced a recurrence that went untreated for at least 4 weeks following onset of the recurrence. The duration of the recurrent episode was examined using survival analytic techniques. Of the 130 subjects, 46 obtained somatic therapy at some time during the course of their depressive illness, while 84 subjects received no somatic therapy throughout their entire depressive episode. Survival analysis, which accounts for these 46 individuals by censoring their episodes at the time treatment was obtained, yielded a median time to recovery of 23 weeks. In the subsample of 84 subjects whose depressive illness went untreated from its inception through its resolution, the median time to recovery was 13 weeks. These results suggest that there is a high rate of recovery in individuals not receiving somatic treatment of their depressive illness, particularly in the first 3 months of an episode. Because treatment-seeking behavior is known to be associated with a worse prognosis, 23 weeks probably represents a lower-limit approximation of the median duration of an untreated depressive episode.

Key Words: Major depression, natural course, untreated, antidepressant.

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Knowledge of the untreated course of an illness serves as a benchmark for measuring the effectiveness of treatment and helps guide scientific inquiry. In the case of major depressive disorder, such knowledge could also assist clinicians and patients in deciding whether or not to initiate antidepressant therapy. Clinically, it would be especially useful to know how long a depressive episode might be expected to last without treatment.

Unfortunately, we have little direct knowledge regarding the untreated course of major depression. Depression is somewhat unique among medical ailments in this regard. While the naturalistic, untreated course of such diseases as syphilis, tuberculosis, and gout have been described in exquisite detail for hundreds and even thousands of years, an accepted definition and standardized outcome criterion set were not established for major depressive disorder until after the introduction of effective treatment.

Knowledge of the untreated course of depression therefore will likely require inferential analyses from studies designed for other purposes. We can identify four such types of studies. First, longitudinal studies conducted prior to the introduction of antidepressant therapy could be reviewed. Second, outcomes for subjects who present for treatment but either do not receive it or are randomized to a wait-list control group could be analyzed. Third, several large scales studies have been conducted in primary care settings to evaluate the impact of improved recognition or delivery of treatment among primary care doctors. The outcomes of subjects whose depression went unrecognized or untreated over the course of follow-up (usually 6–12 months) could be ascertained. Fourth, the untreated course of depression could be gleaned from prospective, observational studies conducted in the community.

Each of these methods has limitations. Subjects who presented for treatment in the era prior to the introduction of antidepressant therapy tended to be the most severely ill, and would not be representative of depressed patients today (Shorter, 1997). Furthermore, standardized diagnostic criteria and outcome measures of depression were not available. Outcomes of subjects who enrolled in a treatment trial and were randomized to a waiting list provide perhaps the most valid insight we have into the naturalistic course of depression, and a meta-analysis of such studies was conducted by one of the authors (Posternak and Miller, 2001). Another study we conducted (Posternak and Zimmerman, 2001) evaluated outcomes of a cohort of depressed patients who presented for treatment but who ended up not receiving antidepressant therapy for a variety of reasons (e.g., never filled prescription, intolerable side effects). Both studies were limited by modest sample sizes ($N = 76$ and $N = 25$, respectively) and their results are, of course, generalizable only to

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treatment-seeking subjects. Observational studies are limited by the nonrandom nature of their design because nontreatment-seeking individuals tend to have a milder depressive illness and experience less psychosocial disruption than treatment-seeking subjects (Coryell et al., 1995).

Considering the widespread availability of antidepressant treatments and the ethical issues involved in randomizing depressed subjects to receive no treatment, it seems unlikely that any future studies will be conducted to evaluate the untreated course of depression. Thus, despite the limitations inherent in each of these methods, they provide perhaps the only insight we will have into the untreated course of depression. Each provides a slightly different perspective, and perhaps as whole they may paint a reasonably accurate picture.

In the present study, we examine the course of illness in 130 subjects who participated in the NIMH sponsored Collaborative Depression Study (CDS) and who did not receive somatic treatment following the onset of a recurrence of unipolar major depression. The CDS is well suited to examine this issue given the standardized diagnostic and follow-up instruments used, the size of the sample, and the length of follow-up.

METHODS

Overview

From 1978 to 1981, individuals receiving inpatient or outpatient treatment of a major mood disorder were recruited into the CDS at academic medical centers in Boston, Chicago, Iowa City (Iowa), New York, and St. Louis. Inclusion criteria included an age of 17 years or more, an IQ greater than 70, the ability to speak English, white race (genetic hypotheses tested), and no signs of a mood or psychotic disorder secondary to a general medical condition. The present study analyzes data from the proband cohort, and does not examine the outcomes from the cohort of relatives. After receiving a complete description of the study, the subjects provided written informed consent, and their subsequent course and treatment have since been recorded. Further details of the study are provided elsewhere (Keller et al., 1992).

Subjects

A total of 955 patients entered the CDS. Within this group, 431 were experiencing an episode of unipolar major depression at intake into the CDS but had no underlying minor depression of at least 2 years' duration, no chronic intermittent depressive disorder, and no history of mania, hypomania, or schizoaffective disorder. Of these 431 subjects, 65 had a diagnosis change to either bipolar or schizoaffective disorder during the follow-up period and were excluded from the analyses in this article. Of the remaining 366 subjects, 318 eventually recovered from the intake episode of major depression during the 15-year follow-up period and were at risk for a recurrence. The other 48 subjects did not recover during the follow-up period for which data are available.

Of the 318 subjects, 130 experienced a recurrence of major depression that went untreated for at least 4 weeks following the onset of the recurrence. Forty-six subjects (35.4%) ultimately obtained somatic therapy at some point during the course of their depressive episode, while 84 subjects did not. The median time to obtaining treatment in these 46 subjects was 62 weeks. These episode durations were censored at the time treatment was obtained just as if the subjects had dropped out of the study. The rationale for including these subjects in the present study is that if we had restricted our analysis only to the 84 entirely untreated subjects, our results would have been skewed to include predominantly those untreated episodes that resolved quickly. For example, an individual who did not receive somatic therapy for their depressive illness and whose episode remitted within 8 weeks would be included in the untreated cohort, but someone who sought treatment after 2 years of unremitting depression would not. Thus, to capture these more refractory untreated cases, we chose to include those untreated individuals who eventually obtained somatic therapy.

Table 1 presents the baseline demographic and clinical features of the entire sample ($N = 130$) as well as the 84 individuals who did not receive somatic therapy throughout the entire course of the depressive episode.

Definition of an Untreated Episode

Information regarding somatic treatment was collected and quantified for each week of the study using the Unipolar Composite Antidepressant (UNICAD) scale (Keller, 1988). The UNICAD employs a 5-point summary scale to rate the intensity of antidepressant somatotherapy received, including electroconvulsive therapy, on a weekly basis. A UNICAD score of 0 means that no somatic treatment was provided, and a UNICAD score of 4 means that treatment equal to a daily dose of 300 mg or more of imipramine or its equivalent was provided. Anxiolytic medications, such as benzodiazepines, were scored on this measure with a rating of 1 to 2 depending on the medication and dosage (Keller et al., 1986). As a strictly observational study, the CDS has not influenced treatment in any way. Of note, psychotherapy was not coded by the UNICAD; therefore, treatment status in the present report refers only to somatic therapy.

A depressive episode was considered untreated and included in the present analysis if UNICAD ratings were 0 for at least the first 4 weeks of the depressive episode. The episode remained untreated as long as UNICAD ratings remained 0. If during any subsequent week a UNICAD rating of 1 or greater was obtained, the depressive episode was censored at the first such instance, as described below.

Since all probands in the CDS were initially recruited while in treatment, the intake episode, by definition, was excluded from our analysis. Following recovery from the index episode, treatment ratings were examined in subjects who experienced one or more recurrences. The first episode of major depression that went untreated by our criteria was included in our analyses. For subjects who had more than one untreated episode ($N = 35$, 11%), only the first such episode was included. In the present report, when recovery occurred without standard antidepressant somatic therapy, we use the term *spontaneous remission* to denote that process.

TABLE 1. Demographic and Clinical Features at Intake of 130 Subjects Who Did Not Receive Somatic Therapy for At Least the First 4 Weeks of Their Depressive Episode, and the 84 Subjects Who Did Not Receive Somatic Therapy Throughout Their Entire Depressive Episode

	Untreated Cohort	Combined Untreated Cohort
	(*N* = 84)	(*N* = 130)
Female, *N* (%)	55 (65.5)	83 (63.8)
Age, y (mean ± *SD*)	33.9 + 13.4	35.2 ± 14.0
Range	17–74	17–74
Marital status, *N* (%)		
Married/living together	34 (40.5)	57 (43.8)
Never married	35 (41.7)	51 (39.2)
Divorced/separated/widowed	15 (17.9)	22 (16.9)
Recruitment setting		
Inpatient	64 (76.2)	97 (74.6)
Outpatient	20 (23.8)	33 (25.4)
RDC endogenous subtype	39 (46.4)	69 (53.1)
Ham-D score	24.8 ± 6.8	25.4 ± 6.5
Comorbid anxiety disorder	31 (36.9)	55 (42.3)
Comorbid substance use disorder	28 (33.3)	47 (36.2)
Education (≥high school diploma), *N* (%)	68 (81.0)	109 (83.8)
History of 3 or more depressive episode at intake, *N* (%)	20 (23.8)	28 (21.5)
Social class (Hollingshead-Redlich Scale)		
I	2 (2.4)	3 (2.3)
II	16 (19.0)	22 (16.9)
III	25 (29.8)	41 (31.5)
IV	28 (33.3)	41 (31.5)
V	13 (15.5)	23 (17.7)
Site		
New York	9 (10.7)	13 (10.0)
St. Louis	29 (34.5)	42 (32.3)
Boston	18 (21.4)	22 (16.9)
Iowa	18 (21.4)	33 (25.4)
Chicago	10 (11.9)	20 (15.4)
Global Assessment of Functioning, mean ± *SD*	44.6 ± 11.4	44.3 ± 11.4
Years of follow-up, mean ± *SD*	12.7 ± 3.8	12.7 ± 3.7

Assessments

Current and past psychiatric histories were assessed at baseline using the Schedule for Affective Disorders and Schizophrenia (Endicott and Spitzer, 1978). Diagnoses were made according to the Research Diagnostic Criteria (RDC; Spitzer et al., 1978), following interviews with probands, and at times, relatives, as well as a review of available medical records.

Follow-up assessments were completed every 6 months for the first 5 years of the study and annually thereafter using the Longitudinal Interval Follow-up Evaluation (Keller et al., 1987). The Longitudinal Interval Follow-up Evaluation is a semistructured instrument that measures numerous clinical variables, including the severity of psychopathology on a weekly basis, and the type and dose of all prescribed psychotropic medications. The severity of psychopathology is quantified on a 6-point scale called the Psychiatric Status Rating (PSR), which can be assigned to any major affective disorder, and which has been shown to have good to excellent interrater and test-retest reliability (Keller et al., 1987; Warshaw et al., 1994). At each interview, the rater assigns a PSR for each week of the study, starting from the last interview. To accomplish this, the rater first reviews the subject's status at the time of the preceding interview, and then identifies chronological anchor points, such as holidays to help the subject remember when significant clinical improvement or deterioration occurred. Patient recall of psychopathology using autobiographical markers of memory (Shum, 1988) has been shown be both reliable and valid (Warshaw et al., 1994; Zimmerman and Coryell, 1986). In addition, corroborative data are obtained from medical records and informants.

A PSR of 1 or 2 is assigned for those weeks in which there are no or minimal symptoms, respectively. A PSR of 3 or 4 corresponds to partial remission or significant symptoms not meeting full criteria for an RDC major affective disorder, respectively. A PSR of 5 is given for those weeks during which subjects meet full criteria for an RDC major affective disorder, and a 6 when accompanied by psychosis or extreme impairment. Recovery from major depression is defined by RDC as beginning with the first of 8 consecutive weeks of no or minimal symptoms (PSR of 1 or 2). Recurrence was defined as the reappearance of RDC major depressive disorder meeting the full criteria for at least 2 consecutive weeks, beginning with the first of these 2 weeks. Recurrence occurred only after the individual had first recovered from his or her preceding mood episode. Episodes of RDC minor depression and chronic intermittent depression were not included in these analyses.

Statistical Analyses

Duration of episodes were examined using survival analytic techniques (Kalbleish and Prentice, 1980). These analyses account for varying lengths of follow-up and estimate the changing probability of recovery at different times over the course of follow-up. The survival time (duration of episode) began at the onset of the major depressive episode. The event that ended each episode was the period of at least 8 consecutive weeks of recovery. The week prior to this 8-week period constituted the final week of the depressive episode. A censored case is one in whom remission was not observed during an untreated interval. Specifically, a case was classified as censored if the subject follow-up ended prior to remission or that subject remained depressed and untreated at the end of the 15-year follow-up period. For the 46 untreated subjects who eventually received somatic therapy, the episode was censored at the time treatment was obtained. In this way, the techniques minimize the effects of censored data by including all subjects who began the observation period regardless of whether they finished it. The cumulative probability of spontaneous remission was estimated with the Kaplan-Meier product limit (Kaplan and Meier, 1958). The interval-specific probabilities of recovery, similar to hazards

represent the proportion of those entering a discrete follow-up interval in a major depressive episode who recovered during the interval.

To examine predictors of recovery, we evaluated seven demographic and clinical features: age (under 30, 30–39, 40–49, and 50 and older), sex, number of lifetime depressive episodes, age of onset of depression, social class, comorbid anxiety disorder, and comorbid substance use disorder. These seven parameters were placed in a Cox regression model, which accounts for independent contributions from each variable.

RESULTS

Figure 1 depicts the course of the 130 subjects inclusive of the 46 depressed subjects who initially went untreated but later sought antidepressant treatment prior to recovery. The median time to recovery in this sample was 23 weeks. The cumulative monthly recovery rates were 15% after 1 month, 26% after 2 months, 38% after 3 months, 52% after 6 months, 70% after 1 year, and 75% after 2 years.

Figure 1 also depicts the time to recovery in the 84 subjects whose depressive illness went untreated from inception through resolution. The median time to recovery in this cohort was 13 weeks. The cumulative monthly recovery rates were 23% after 1 month, 37% after 2 months, 52% after 3 months, 67% after 6 months, and 85% and 89% after 1 and 2 years, respectively. Spontaneous remission was most likely to occur in the first 3 months following onset: in the first 3 months, 52% of the subjects recovered, whereas only 15%, 8%, and 10% recovered in the three subsequent 3-month periods.

In examining predictors of recovery, we found that age ($\chi^2 = 14.7$, $df = 3$, $p = 0.002$) but not sex, number of prior episodes, age of onset, social class, or comorbid anxiety or substance use disorders were significantly associated with spontaneous recovery. Specifically, compared with the 30to 39 cohort, subjects under age 30 were twice as likely to recover (OR = 2.0, CI = 1.1–3.9), and subjects aged 40 to 49 were five times more likely to recover (OR = 5.3, CI = 2.1–13.8). It is unclear whether this unexpected finding represents a spurious finding or a true distinction in recovery rates.

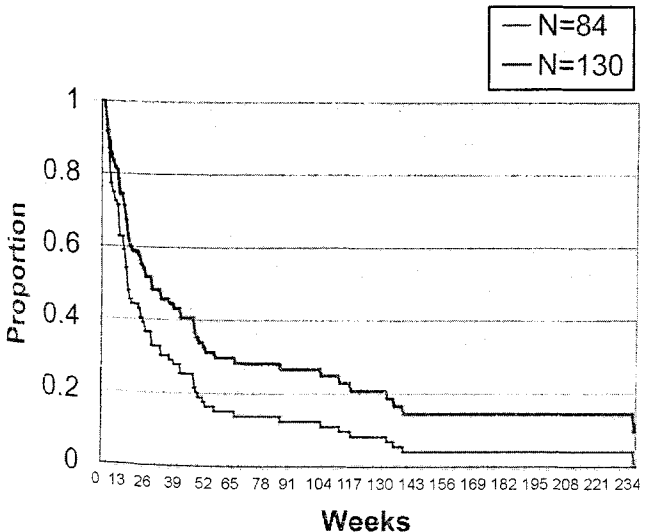

FIGURE 1. Survival curves for 84 subjects who received no somatic therapy throughout their entire depressive episode and 130 subjects inclusive of 46 subjects who eventually obtained somatic therapy.

DISCUSSION

While the waxing and waning course of major depression has long been recognized, surprisingly little attention has been paid to the occurrence of spontaneous remission. Kraepelin speculated that left untreated, major depressive episodes would tend to last about 6 to 8 months in most cases (Kraepelin, 1921). Subsequent reports have generally supported this assertion (Angst, 1986; Hohman, 1937; Huston and Locher, 1948; Rennie and Fowler, 1942; Shobe and Brion, 1971), though these studies were largely based on clinical observation and retrospective analyses. The present study provides perhaps the most methodologically rigorous confirmation of this estimate.

The major limitation of the present study is that subjects were not randomized to receive no treatment. Depressed individuals who do not receive somatic treatment have been shown to experience less economic disruption as a result of their illness compared with treatment-seeking patients (Coryell et al., 1995). In assessing time to recovery in a cohort of subjects from the CDS that included both subjects who had and had not received somatic treatment of their depressive illness, Keller et al. (1992) reported recovery rates of 19% within 4 weeks, 31% within 8 weeks, 41% within 13 weeks, 54% within 26 weeks, and 70% within 1 year. Since subjects who did not receive somatic therapy from the present analysis recovered more quickly from their depressive episode, this suggests that non-treatment-seeking individuals have an inherently better prognosis than treatment-seeking individuals. Thus, our results cannot necessarily be generalized to the treatment-seeking population.

For this reason, we would posit that 23 weeks is a lower limit approximation of the median duration of major depression in the absence of somatic therapy. Because we have insufficient data regarding the course of untreated major depression in the treatment-seeking population, and because chronicity is likely to be overrepresented in this cohort, we do not know whether the natural duration of major depression is significantly longer than 23 weeks.

Our analysis of the subgroup of depressed subjects who went without somatic therapy throughout the entire course of their depressive illness yielded a median episode duration of 13 weeks—nearly identical to what Coryell et al. (1995) reported in a separate cohort of subjects who did not receive somatic treatment. Subsequent to the first 3 months of illness, the spontaneous remission rate appears to decrease dramatically, though a substantial number continue to recover so that by the end of 1 year, only 15% of the subjects who had not received any antidepressant medication treatment were still depressed.

Such a high spontaneous remission rate may explain why studies conducted in primary care settings aimed at increasing the detection of major depression (Coyne et al.,

1997; Ormel et al., 1991; Schulberg et al., 1987; Simon et al., 1999; Tiemens et al., 1996, 1999), or using more aggressive treatment (Koenig et al., 1989; Magruder-Habib et al., 1989; Schulberg et al., 1997; Simon et al., 1995), have often failed to demonstrate improved outcomes compared with usual care. If as many as 85% of depressed individuals who go without somatic treatment spontaneously recover within 1 year, it would be extremely difficult for any intervention to demonstrate a superior result to this. We would recommend, as has been suggested elsewhere (Coryell et al., 1994), that such studies consider including only patients who have been depressed for a minimum of 3 months, since it is during this time that spontaneous remission is most likely to occur.

Our results also allow us to estimate the percentage of subjects enrolled in controlled treatment trials who experience a spontaneous remission of symptoms. If 50% of depressed individuals spontaneously recover within 6 months, then the spontaneous remission rate of depression would be about 2% per week during this time frame. An estimate of the naturalistic course of depression in treatment-seeking individuals was put forth in a recent meta-analysis that evaluated the outcomes of depressed subjects who were randomized to a no-treatment control group (Posternak and Miller, 2001). The authors reported that 15 of 76 (19.7%) subjects who were randomized to a wait-list control group experienced a spontaneous remission of symptoms over an average of 10 weeks—which again translates into a 2% weekly spontaneous remission rate. If this figure is accurate, then 12% to 16% of subjects enrolled in standard antidepressant efficacy trials might be expected to experience spontaneous remission during the course of a treatment trial of 6 to 8 weeks—irrespective of whether they are randomized to active medication or placebo. Because *remission* of symptoms signifies greater improvement than *response* (usually defined as a $\geq$50% reduction in symptom severity), the percentage of spontaneous responders may even be higher. Thus, spontaneous improvement may account for a significant proportion of the 30% to 35% placebo response rate that is typically reported in antidepressant trials, as has similarly been suggested elsewhere (Hrobjartsson and Gotzshce, 2001).

Several limitations to the present study should be kept in mind. First, subjects were not randomized to receive or not receive somatic therapy, and our results can not be generalized to the treatment-seeking population. Second, psychotherapy was not accounted for in our assessment of treatment status, and it is likely that some subjects who we have labeled as untreated were actually receiving psychotherapy. Two recent studies, however, suggest that only a small percentage (around 10%) of depressed patients treated in the community receive psychotherapy alone (i.e., without somatic therapy; Greenfield et al., 2000; Parker et al., 2001). A third limitation is that subjects in the present study were recruited from psychiatric settings and not through primary care doctors. Thus, any extrapolation of our results to the primary care setting should be done cautiously, especially since depressed patients with medical comorbidity may have a worse prognosis (Keitner et al., 1992). Fourth, all subjects were initially recruited from academic centers, and such patients may differ from those treated in the community. Fifth, because our goal was to examine prospectively the course of major depression in the absence of somatic therapy, our analyses focused on the first depressive recurrence that went untreated and excluded the intake episode. Thus, our results may not generalize to first episodes. Furthermore, 48 of 366 subjects never recovered from their intake episode, and this refractory cohort could not be accounted for in our analyses.

Finally, it should also be pointed out that the present study did not examine the risk for recurrence, which may be as high as 50% in the first year following recovery (Coryell et al., 1991; Faravelli et al., 1986; Keller et al., 1983; Ramana et al., 1995). Because antidepressant treatment has been shown to reduce the risk of recurrence (Maj et al., 1992; Viguera et al., 1997), it is possible that patients whose depressive illness spontaneously remits might still benefit from such treatment as prophylaxis against future recurrences.

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