PART I

DESCRIPTIVE ASPECTS OF DEPRESSION

Depression is one of the most common psychiatric disorders and, from a societal perspective, is perhaps the most costly. Depression is also a highly recurrent disorder with an increasingly younger age of onset for the initial episode. In the six chapters in this part, the authors discuss issues concerning the onset and course of depression, its prevalence and societal costs, and important factors involved in studying this disorder. Kessler (Chapter 1) describes epidemiological aspects of depression: its prevalence and its economic cost. Boland and Keller (Chapter 2) discuss the course and outcome of this disorder, describing the results of several large-scale longitudinal investigations that have monitored the course of depression over many years. Nezu, Nezu, McClure, and Zwick (Chapter 3) describe the most widely used interview-based and self-report measures of depression, and discuss important issues involved in the assessment of this disorder. Extending this discussion, Ingram and Siegle (Chapter 4) describe a number of methodological issues in the study of depressive disorders, and make several noteworthy recommendations concerning how research in this area might proceed most fruitfully. Klein, Durbin, Shankman, and Santiago (Chapter 5) then describe the nature of the relation between depression and various aspects of personality functioning. Finally, Johnson and Kizer (Chapter 6) discuss similarities and differences in the clinical phenomenology and psychosocial predictors of unipolar and bipolar depression.

1

Epidemiology of Depression

Ronald C. Kessler

The first modern North American general population epidemiological surveys that included information about depression were carried out in the late 1950s in the Midtown Manhattan Study (Srole, Langner, Michael, Opler, & Rennie, 1962) and the Stirling County Study (Leighton, Harding & Macklin, 1963). These early surveys used dimensional screening scales of nonspecific psychological distress to pinpoint respondents with likely mental disorders and then administered clinical interviews to these respondents. The outcome of primary interest was a global measure of mental disorder rather than individual diagnoses. No prevalence estimates of depression were reported. However, the screening scales in these studies included a number of items that assessed depressed mood and other symptoms that have subsequently come to be seen as part of the depressive syndrome. It is possible to make rough estimates about the prevalence and correlates of depressive disorders from these data (Murphy, Laird, Monson, Sobol, & Leighton, 2000).

In later surveys, variants on the screening scales used in the Midtown Manhattan and Stirling County studies were generally used without clinical follow-up. (See Link & Dohrenwend, 1980, for a review.) Scale scores were sometimes dichotomized in order to define "cases" of mental disorder based on some external standard of a clinically relevant cutpoint, although there was ongoing controversy about the appropriate decision rules for defining cases (Seiler, 1973). In order to resolve this controversy, structured diagnostic interviews appropriate for use in community surveys were developed in the late 1970s. The Diagnostic Interview Schedule (DIS; Robins, Helzer, Croughan, Williams, & Spitzer, 1981) was the first of these instruments. Dimensional screening scales continued to be widely used to screen for mental illness in primary care (Goldberg, 1972) and to assess symptom severity and treatment effectiveness among patients in treatment for mental disorders (Derogatis, 1977) even after the introduction of the DIS. However, psychiatric epidemiologists, influenced by the widely published results of the Epidemiologic Catchment Area Study (Robins & Regier, 1991), which was based on the DIS, abandoned the study of dimensional distress measures in favor of dichotomous caseness classifications in general population surveys.

We now have had 2 decades of experience with community epidemiological surveys using fully structured diagnostic interviews like the DIS and the more recently developed CIDI (Robins et al., 1988), PRIME-MD (Spitzer et al., 1994), and MINI (Sheehan, Lecrubier,

Sheehan, Amorim, & Janavs, 1998). It is clear from this experience that fully structured diagnostic interviews, while very useful, are inadequate by themselves to provide the information needed by health policy planners on the magnitude of the problem of untreated serious depression. The reason for this is that the DSM and ICD criteria are so broad that close to half of the people in the general population receive one or more diagnoses on a lifetime basis (Kessler et al., 1994) and close to one-fifth at any one point in time (Kessler & Frank, 1997). With prevalences as high as these, the dichotomous caseness data provided in diagnostic interviews need to be supplemented with dimensional information on severity to be useful to health policy planners (Regier et al., 1998).

Unfortunately, the most recently available adult general population epidemiological data on the prevalence of major depression do not include dimensional severity measures. This is an especially important omission in light of the suggestion by some commentators that the majority of community cases who meet criteria for major depression have fairly mild disorders (Regier, Narrow, Rupp, Rae, & Kaelber, 2000). The World Health Organization (WHO) is currently carrying out a massive worldwide epidemiological survey of mental disorders, known as the World Mental Health 2000 (WMH2000) Initiative, that aims to correct this problem by evaluating a wide range of mental disorders both with dichotomous diagnostic measures and with dimensional clinical severity measures (Kessler & Ustun, 2000). However, WMH2000 results will not be available for another 2 years.

The first section of this chapter presents a broad overview of the main findings in the literature regarding the descriptive epidemiology of major depression. The overview is brief because much of this literature has recently been reviewed elsewhere (Lewinsohn, Rohde, Seeley, Klein, & Gotlib, 2000; Merikangas, 2000; Blazer, 2000; Horwath & Weissman, 1995; Bland, 1997). The second section of the chapter addresses the issue of severity by reviewing available data on the consequences of depression as assessed in community surveys. The third section, finally, reviews epidemiological data on patterns of help seeking for depression.

DESCRIPTIVE EPIDEMIOLOGY

Point Prevalence

Community surveys that assess depression with symptom screening scales find that up to 20% of adults and up to 50% of children and adolescents report depressive symptoms during recall periods between 1 week and 6 months (Kessler, Avenevoli, & Merikangas, 2001). There is a U-shaped distribution of mean scores in these surveys in relation to age, with the highest scores found among the youngest and the oldest respondents and the lowest scores found among people in midlife (Kessler, Foster, Webster, & House, 1992). Point prevalence estimates for DSM major depression in surveys that use structured diagnostic interviews are considerably lower. Rates of current major depression are typically less than 1% in samples of children (reviewed by Merikangas & Angst, 1995), as high as 6% in samples of adolescents (reviewed by Kessler, Avenevoli, & Merikangas, 2001), and in the range 2–4% in samples of adults (WHO International Consortium in Psychiatric Epidemiology, 2000).

The discrepancy between the high prevalence of symptoms in screening scales and the comparatively low prevalence of depressive disorders means that many people have subsyndromal depressive symptoms. Recent epidemiological studies have started to investigate these subsyndromal symptoms using the diagnostic criteria for minor depression and recurrent brief depression (RBD) stipulated in DSM-IV-TR (American Psychiatric Association, 2000). Major depression (MD) requires 2 weeks of clinically significant dysphoria or anhe-

donia (or irritability among children) along with a total of five symptoms. Minor depression (mD), in comparison, requires two to four symptoms with the same severity and duration requirements as MD, while RBD requires the repeated occurrence of the same number and severity of symptoms as MD for several days each month over the course of a full year. These recent studies have documented rates of subsyndromal depression among both adolescents (Gotlib, Lewinsohn, & Seeley, 1995; Kessler & Walters, 1998) and adults (Judd, Akiskal, & Paulus, 1997; Kessler, Zhao, Blazer, & Swartz, 1997) that are as high as, if not higher than, the rates of MD. In addition, a longitudinal study of adolescents followed into adulthood found that subsyndromal depression is a powerful predictor of the subsequent onset of MD (Angst, Sellaro, & Merikangas, 2000).

Subtypes

A number of proposals have been made to subtype the diagnosis of MD based on symptom profiles (reviewed by Kendell, 1976). The only stable subtyping distinction that has emerged consistently in empirical epidemiological studies, however, is between depression with vegetative symptoms (e.g., weight loss, insomnia, appetite loss) and reverse vegetative symptoms (e.g., weight gain, hypersomnia, appetite increase) (Davidson, Woodbury, Pelton, & Krishnan, 1988; Eaton, Dryman, Sorenson, & McCutcheon, 1989). Between one-fourth and one-third of all people with MD have a reverse vegetative symptom profile, with some evidence that this atypical depression is more common among women than men and more strongly associated than vegetative depression with a family history of depression. There is little evidence, in comparison, that atypical depression is more persistent or severe than typical depression. Indeed, in one recent analysis of depression subtyping, typicality and severity emerged as separate and largely independent subtyping dimensions (Sullivan, Kessler, & Kendler, 1998).

Another important subtyping distinction concerns the existence of cyclical depression. Two cycling depressive subtypes have been identified: seasonal affective disorder (SAD; Rosenthal et al., 1984) and premenstrual mood disorder (PMD; Halbreich, 1997). Community surveys find that 10% or more of people in the general population report seasonal variations in depressed mood and related symptoms (e.g., Booker & Hellekson, 1992; Rosen et al., 1990). Seasonal depression is typically most common in the winter months and more prevalent in northern than southern latitudes. However, the prevalence of narrowly defined DSM seasonal affective disorder, which requires a lifetime diagnosis of recurrent MD or mD and at least two-thirds of all episodes following a seasonal pattern, is much less common. Blazer, Kessler, and Swartz (1998) found that only 1% of the population meet narrowly defined criteria for SAD, representing only about 5% of all people with mD or MD. Among people with clinical depression, Blazer et al. found that SAD was somewhat more common among men than women and older than younger respondents.

Community surveys show that the majority of women report experiencing some symptom changes associated with their menstrual cycles (Pearlstein & Stone, 1998; Olive, 1991). Only between 4 and 6%, however, report what appears to be a PMD (Sveindottir & Backstrom, 2000). A diagnosis of PMD requires a clear and recurring pattern of onset and offset of five or more mood and related symptoms at specific points in the majority of menstrual cycles over the course of a full year. Assessments with daily mood diaries over two or more menstrual cycles (Freeman, DeRubeis, & Rickels, 1996) typically show that only about half of the women who report cyclical mood problems actually suffer from PMD. The others have more chronic syndromal or subsyndromal mood disorders that are sometimes exacerbated by menstrual symptoms. There is currently a great deal of interest in PMD among depression researchers based on evidence of family aggregation with major depression

(Yonkers, 1997) and responsiveness to selective serotonin reuptake inhibitors but not tricyclic antidepressants (Freeman, Rickels, Sondheimer, & Polansky, 1999). However, there is also controversy regarding appropriate diagnostic and assessment criteria (Severino, 1996). Community epidemiological data are scant due to the logistic complications created by the fact that a definitive diagnosis requires the collection of daily mood diaries across two or more menstrual cycles. Such diaries are typically collected only in clinical samples, although there are a few small community surveys that have collected diary data as well (e.g., Sveindottir & Backstrom, 2000). Given the existence of so many uncertainties in this area of investigation, a large representative epidemiological survey of PMS using dairy methods would be very valuable.

Lifetime Prevalence

Epidemiological surveys that administer diagnostic interviews generally assess lifetime prevalences of MD and estimate age of onset distributions from retrospective reports (e.g., Christie et al., 1988). Lifetime prevalence estimates of MD in U.S. surveys have ranged widely, from as low as 6% (Weissman, Bruce, Leaf, Florio, & Holzer, 1991) to as high as 25% (Lewinsohn, Rohde, Seeley, & Fischer, 1991). The only nationally representative general population data in the United States based on a structured diagnostic interview come from the National Comorbidity Survey (NCS; Kessler et al., 1994), where 15.8% of respondents met criteria for a lifetime MD episode and an additional 10.0% of respondents met criteria for lifetime mD (Kessler, Zhao, et al., 1997).

The wide variation in prevalence estimates across surveys is probably due to a combination of at least three factors. First, as discussed in more depth below, the prevalence of depression has probably increased in recent cohorts. This means that earlier surveys would be expected to have lower prevalence estimates than more recent surveys. Second, reluctance to admit depression has decreased in recent cohorts, which will also increase prevalences in more recent surveys. The third factor involves an important methodological difference between the diagnostic interviews that were used in early surveys based on the Epidemiologic Catchment Area (ECA) program (Robins & Regier, 1991), which uniformly produced very low prevalence estimates, and the more refined diagnostic interviews used in recent surveys such as the NCS, the Mental Health Supplement to the Ontario Health Survey (Offord et al., 1994), and the Mexican-American Prevalence and Services Survey (Vega et al., 1998). Both types of interviews use a stem–branch structure to assess mental disorders. In this approach, respondents are first asked one or more initial questions about core symptoms of the disorder under investigation. For example, a stem question for MD might be "Did you ever have a time lasting 2 weeks or longer when you felt sad or depressed most of the day nearly every day"? The respondents who are affirmative are then administered a more detailed set of follow-up questions that assess all criteria of the disorder. This same stem–branch approach is used to assess each of the dozen or more diagnoses evaluated in the surveys.

While both the type of interview used in the ECA and the type of interview used in the NCS were based on this stem–branch structure, only the NCS interview was designed to minimize the underreporting problems that methodological studies have shown to occur in interviews of this sort. A detailed discussion of the instrument design issues is presented elsewhere (Kessler, Wittchen, Abelson, & Zhao, 2000). In brief, methodological studies show that stem–branch questions are prone to two types of underreporting bias (Bradburn, Sudman, & Associates, 1979; Turner & Martin, 1984). One is that some respondents underreport stem questions once they recognize that positive responses lead to more detailed questions. The other is that most respondents fail to appreciate the cognitive complexity of

the memory search involved in answering stem questions that require lifetime recall. These problems were addressed in the NCS by developing a Life Review Section near the beginning of the interview that included the stem questions for all the disorders assessed in the survey. The respondent instructions in this section were designed to facilitate and motivate active memory search. This entire section was administered before probing any positive stems, thus avoiding conscious nondisclosure once respondents recognized that positive stem responses led to further questioning. A field experiment carried out after the completion of the NCS randomly assigned respondents to either asked stem-and-branch questions in sequence throughout the interview or a version that included the Life Review Section and then validated diagnoses with clinician-administered reinterviews. Two important results emerged from this experiment. First, the Life Review Section was found to increase the prevalence estimates of depression and other disorders enough to explain the large observed differences in prevalence estimates between the ECA and the NCS. Second, the clinical reinterviews showed that the additional cases discovered with the Life Review Section were genuine cases of depression rather than false positives (Kessler, Wittchen, et al., 1998).

Based on these results, it seems safe to conclude that at least one out of every six adults in the U.S. population has met criteria for an MD episode at some time in their life and one in four has met criteria for either MD, mD, or recurrent brief depression. It is important to recognize, though, that these are estimates of prevalence-to-date risk rather than lifetime risk. Kaplan–Meier (KM) age-of-onset curves can be used to generate lifetime risk estimates. As shown in Figure 1.1, which presents KM curves separately for MD and mD based on the NCS data, the lifetime risk projections based on these curves are considerably higher than the lifetime-to-date prevalence estimates.

In evaluating the KM curves in Figure 1.1, it is important to recognize that the lifetime risk projections they generate are based on the assumption that conditional risk of first onset at given ages is constant across cohorts. This assumption is incorrect. As shown in

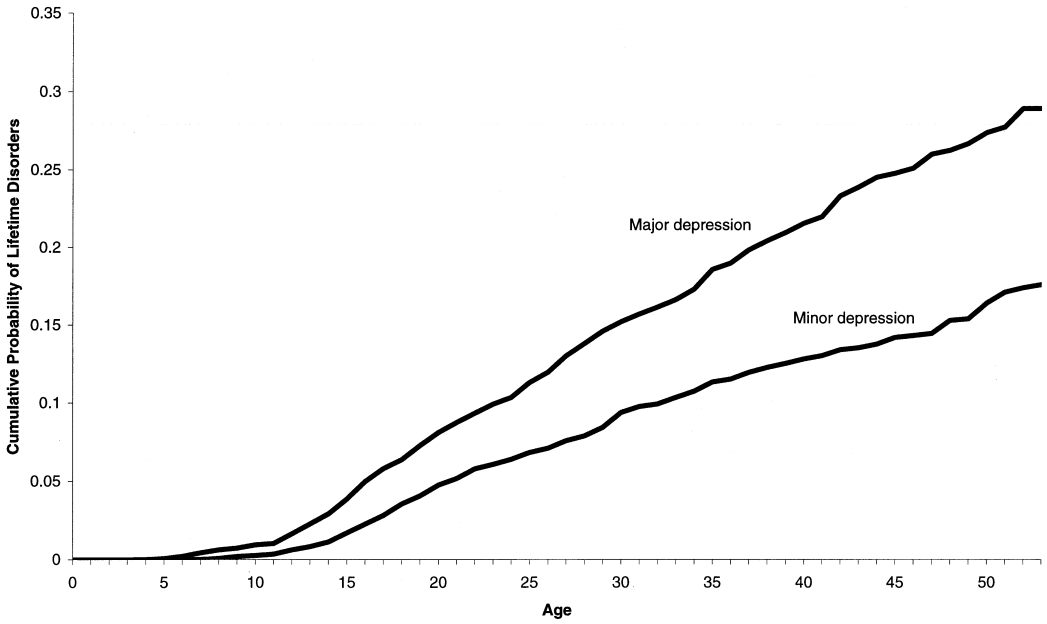

FIGURE 1.1. Age of onset of major and minor depression in the NCS.

Figure 1.2, the KM curves for MD and mD combined in the NCS differ substantially by cohort. The same general pattern holds when we examine MD and mD separately (Kessler, Zhao, et al., 1997). This pattern of intercohort variation could be due to the risk of depression increasing in successively more recent cohorts. Other possible causes are that willingness to admit depression in a survey might have increased in recent cohorts (Kessler, 2000a) and that forgetting a past history of depression might increase with age (Giuffra & Risch, 1994). There is no way to adjudicate among these contending interpretations definitively with available data, although indirect evidence strongly suggests that at least part of the apparent cohort effect is due to a true increase in risk of depression in recent cohorts (Weissman & Klerman, 1992).

Course

Little longitudinal research has been done to study the course of depression in general population samples (but for important exceptions, see Angst & Merikangas, 1997; Lewinsohn et al., 2000). However, cross-sectional surveys consistently find that the prevalence ratio of 12-month MD versus lifetime MD is in the range between .5 and .6 (Kessler, McGonagle, Swartz, Blazer, & Nelson, 1993; Weissman et al., 1991). This means that between half and two-thirds of people who have ever been clinically depressed will be in an episode in any given year over the remainder of their lives. At least three separate processes contribute to the size of this ratio: the probability of a first episode becoming chronic; the probability of episode recurrence among people with a history who are not chronically depressed; and speed of episode recovery among people with recurrent episodes.

Epidemiological studies show that the first of these three processes is quite small, with only a small fraction of 1% of people in the population reporting a single lifetime depressive episode that persists for many years (Kessler et al., 1993). The prevalences of dysthymia

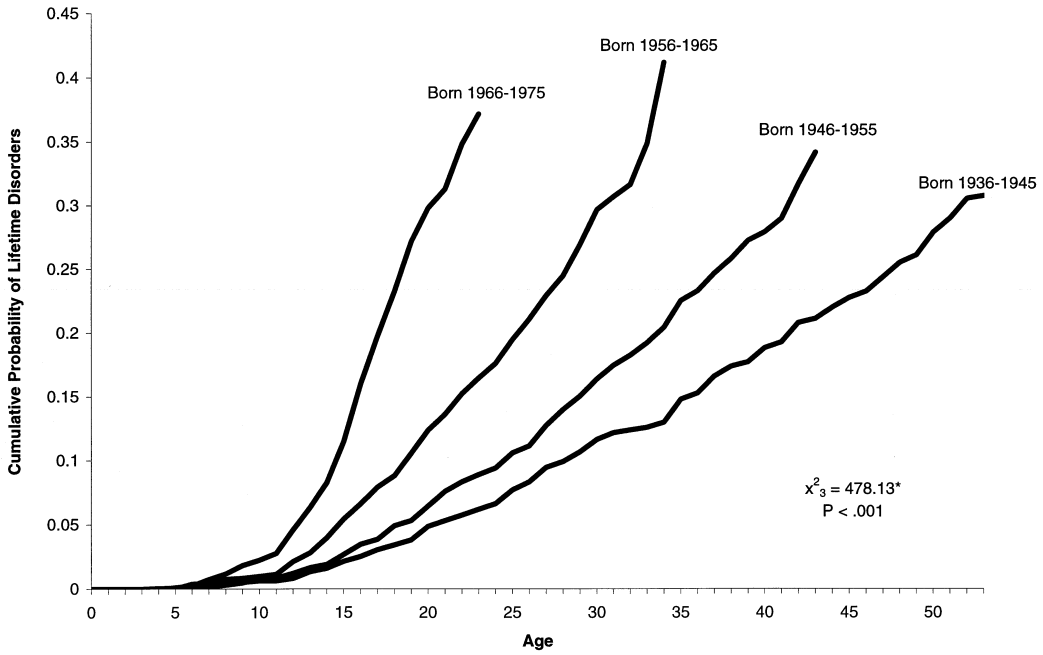

FIGURE 1.2. Age of onset of major and minor depression by cohort in the NCS.

and chronic mD are somewhat higher, but still only in the range 3–4% combined in the total population (Kessler et al., 1994). Episode recurrence, in comparison, is very common, with more than 80% of people with a history of MD having recurrent episodes. In the NCS, the median number of episodes was seven among respondents with an age of first onset more than a decade prior to the interview. Moreover, over 90% of all episodes in the year prior to the interview were recurrences rather than first onsets. Speed of episode recovery, finally, appears to be highly variable, although the epidemiological evidence is slim. Only two large community surveys have studied speed-of-episode recovery. One found that 40% of cases of MD recovered by 5 weeks and over 90% by 1 year (McLeod, Kessler, & Landis, 1992). The other found that the median time to recovery was 6 weeks, with over 90% recovered within a year (Kendler, Walters, & Kessler, 1997). Very few of the people with short episodes ever come to clinical attention, which means that time to recovery is considerably longer in clinical samples (e.g., Brugha et al., 1990).

Distinguishing First Onset from Recurrence

It is important to distinguish between first onset and recurrence in studying the predictors of depression episode onset because the two types of episodes have different predictors (Lewinsohn, Allen, Seeley, & Gotlib, 1999). For example, women are nearly twice as likely as men to become depressed for the first time, while most epidemiological studies find no sex difference in recurrence risk (Kessler et al., 1993). History of depression is not only a powerful predictor of episode onset, but it is also strongly related to stressful events such as divorce and job loss and to presumed stress buffers such as social support and neuroticism (Kessler & Magee, 1993). Because of these relationships with all three of the main variables in models of the relationship between stress and depression (i.e., stress, stress buffers, and depression), failure to control for history of depression can lead to substantial bias in stress models. Yet most epidemiological studies that attempt to discover risk factors for episode onset of depression fail to include a control for history of prior episodes (Kessler, 1997a). A complicating factor is that risk of spontaneous recurrence of depressive episodes increases with number of prior episodes (Ghaziuddin, Ghaziuddin, & Stein, 1990). This means that it is important not only to control for history of depression in studies of the predictors of episode onset, but also to control for number of prior episodes and to estimate interactions between number of prior episodes and other predictors (Hammen & Gitlin, 1997).

Comorbidity

Studies of diagnostic patterns in community samples show that there is substantial lifetime and episode comorbidity between depression and other mental and substance use disorders. Indeed, comorbidity is the norm among people with depression. The ECA study found that 75% of respondents with lifetime MD also met criteria for at least one of the other DSM-III disorders assessed in that survey (Robins, Locke, & Regier, 1991), while the comparable proportion of DSM-III-R (American Psychiatric Association, 1987) comorbidity in the NCS was 74% (Kessler, 1995). There is controversy concerning the extent to which these high rates of comorbidity are artifacts of changes in the diagnostic systems used in almost all recent studies of comorbidity (Frances et al., 1992). In the United States, these systems, beginning with DSM-III (American Psychiatric Association, 1980) and continuing through DSM-IV-TR (American Psychiatric Association, 2000), dramatically increased the number of diagnostic categories and reduced the number of exclusion criteria so that many people who would have received only a single diagnosis in previous systems now receive multiple diagnoses. The intention was to retain potentially important

differentiating information that could be useful in refining understanding of etiology, course, and likely treatment response (First, Spitzer, & Williams, 1990). However, it could also be argued that it had the unintended negative consequence of artificially inflating the estimated prevalence of comorbidity.

This uncertainty will presumably be resolved in the future by using established criteria to determine the validity of diagnostic distinctions (Cloninger, 1989). Until that time, though, we are left with a situation in which it appears that depression is highly comorbid with a number of other disorders. The strength of these comorbidities is remarkably consistent between the ECA and NCS surveys, the two largest general population surveys in the United States that have estimated comorbidities among DSM disorders (Kessler, 1995). The strongest lifetime comorbidities (odds ratios) of depression in both these surveys are with anxiety disorders, especially generalized anxiety disorder (6.0), panic disorder (4.0), and posttraumatic stress disorder (4.0), although less powerful but still significant comorbidities are found with a wide range of other mental disorders (Kessler, 1997b). Episode comorbidities are generally somewhat stronger, indicating that comorbidity is associated with recurrence risk (Kessler, 1995).

The majority of comorbid depression is temporally secondary in the sense that the first onset of depression occurs subsequent to the first onset of at least one other comorbid disorder, although this is more true among men than among women. Survival analysis of the cross-sectional NCS data using retrospective age-of-onset reports to determine temporal priority shows that a wide range of temporally primary anxiety, substance abuse, and other disorders predict the subsequent first onset of depression (Kessler et al., 1996). Time-lagged effects are strongest for generalized anxiety disorder (7.6) and simple phobia (4.2). There is little evidence of change in these odds ratios as a function of time since onset of the primary disorder. This absence of a time gradient is inconsistent with the hypothesis that secondary depression is a general exhaustion response to unremitting anxiety (Akiskal, 1990). At the same time, most of these odds ratios are confined to effects of active primary disorders as opposed to remitted primary disorders. This means that people who currently have these other disorders are at risk of depression. The fact that history of remitted anxiety is generally not associated with risk of depression suggests indirectly that anxiety is a risk factor rather than a risk marker. Two important exceptions, though, are early-onset simple phobia and panic, both of which appear to be markers rather than risk factors. The key evidence here is that people with a history of these disorders have elevated risk of subsequent first onset of depression even when the primary disorders are no longer active (Kessler et al., 1996).

THE CONSEQUENCES OF DEPRESSION

Psychiatric epidemiologists have traditionally been much more interested in estimating prevalences and discovering modifiable risk factors (e.g., Eaton & Weil, 1955) than in studying the consequences of mental illness (e.g., Faris & Dunham, 1939). This situation has changed in the past decade, though, as the managed care revolution and the rise of evidence-based medicine have made it necessary to document the societal costs of illness (Gold, Siegel, Russell, & Weinstein, 1996). Depression has emerged as an important disorder in this new work. Indeed, the World Health Organization Global Burden of Disease (GBD) Study ranked depression as the single most burdensome disease in the world in terms of total disability-adjusted life years among people in the middle years of life (Murray & Lopez, 1996). This top ranking was due to a unique combination of high life-

time prevalence, early age of onset, high chronicity, and high role impairment (Kessler, 2000c).

Role Impairment

It was noted in the introduction that the estimated prevalence of depression and other mental disorders in recent epidemiological surveys has been so high that some commentators have speculated that most must be mild cases (e.g., Regier et al., 2000). This speculation is superficially inconsistent with the GBD conclusion that depression is associated with more societal burden than any other condition. However, the GBD relied on expert opinion rather than epidemiological data to rank-order the impairments of chronic conditions. The expert raters were most familiar with clinical cases. It is possible that the cases found in community surveys are less seriously impaired.

The Medical Outcomes Study (Wells et al., 1989) collected data on this issue by screening samples of primary care patients for a small number of sentinel conditions that included MD and following these patients over time to evaluate their medical costs and role functioning. The role impairments caused by depression were comparable to those caused by seriously impairing chronic physical disorders. Similar results were found in the nationally representative general population sample assessed in the MacArthur Foundation's Midlife Development in the United States (MIDUS) survey. The MIDUS results suggest that the role impairments caused by depression are comparable to those caused by such chronic physical disorders as arthritis, asthma, diabetes, and hypertension (Kessler, Mickelson, Barber, & Wang, 2001).

A substantial part of the role impairment caused by depression involves reduced work performance. A recent economic analysis of the costs of depression in the workplace estimated that the annual salary-equivalent costs of depression-related lost productivity in the United States exceeds $33 billion (Greenberg, Kessler, Nells, Finkelstein, & Berndt, 1996). This is an underestimate of the overall workplace costs of depression because it excludes such potentially important components as the effects of depression on the performance of coworkers, industrial accidents, and turnover. It is important to note that these effects of depression on work performance disappear among remitted cases (Kessler & Frank, 1997), suggesting that effective depression treatment would reduce workplace costs. Simulations suggest that employers could recover between 45% and 90% of the direct treatment costs of depression in improved salary-equivalent work performance over the course of a single year (Kessler, Barber, et al., 1999). It is plausible to imagine that a complete cost accounting that considered the effects of depression on a broader set of workplace outcomes would show that the direct costs of depression treatment are fully offset by decreased indirect workplace costs. A definitive effectiveness trial to evaluate this hypothesis has not yet been carried out, although depression treatment trials have consistently documented significant effects of treatment on work outcomes (Mintz, Mintz, Arruda, & Hwang, 1992; Wells et al., 2000).

Role Transitions

It was noted in the discussion of the GBD study that depression has a unique constellation of characteristics leading to its rating by the World Health Organization as the single most burdensome chronic condition in the world among people in the middle years of life. Perhaps the most important of these is early age of onset. The median age of onset of MD (see Figure 1.1) is in the mid-20s. This is at least 2 decades earlier than the median ages

of onset of the chronic physical disorders that have prevalences and impairments comparable to those of depression. One important implication of this early age of onset is that depression, unlike most chronic physical disorders, occurs at a time in the life course when it can have a profound effect on critical life course role transitions. The latter include educational attainment, entry into the labor force, parenting, and marital timing and stability.

A series of analyses based on the NCS used retrospectively dated age of onset reports to estimate the effects of depression and other mental disorders on early life role transitions. An investigation of the effects of early-onset depression on educational attainment found that depression prior to completing high school significantly predicted (odds ratio) high school dropout (1.5) and, among high school graduates, predicted failure to enter college (1.6) (Kessler, Foster, Saunders, & Stang, 1995). Depression as of the age of high school completion powerfully predicted college dropout among respondents who went to college (2.9). A separate investigation of the effects of early-onset depression on teen childbearing found that depression is associated with a 2.2 relative odds of teenage pregnancy among both girls and boys as well as with elevated rates of failure to contracept (Kessler, Berglund, et al., 1997). An investigation of the effects of early-onset depression on marital timing and stability, finally, found that prior depression predicts both teenage marriage (2.3) and subsequent divorce (1.7) (Kessler, Walters, & Forthofer, 1998).

It is important to appreciate that this constellation of truncated education, early childbearing, and marital instability are central components of welfare dependency. It is little wonder, then, that the welfare-to-work experiments that have been carried out in conjunction with recent state welfare reform programs have documented high rates of depression among welfare mothers and significant adverse effects of maternal depression on making a successful transition from welfare to work (Danziger et al., 2000; Olson & Pavetti, 1996). This is another example of a case in which the societal costs of not treating depression may be greater than the costs of treatment. We are unaware, though, of any trial to evaluate the cost-effectiveness of providing mental health treatment as a component of the services provided to welfare mothers to facilitate the transition from welfare to work.

Other Adverse Consequences of Depression

It was noted in the last subsection that the financial savings to the employer due of increased work productivity with the remission of depression might approach or exceed the direct costs of treating depressed workers. The critical experiment needed to test this hypothesis has not yet been carried out. However, another type of experiment has been carried out that documents a cost saving of depression treatment for managed care. Specifically, services research shows that people with untreated depression are often heavy users of primary care medical services for vaguely defined physical complaints. This observation has led some clinical researchers to speculate that systematic screening, detection, and treatment of primary care patients with depression might lead to an overall reduction in primary care costs. A series of experiments have shown that a partial offset effect of this sort exists (Katon et al., 1996; Katzelnick et al., 2000). The vast majority of depressed patients detected in primary care screening accept treatment for their depression. The average total cost of these patients to the managed care system exclusive of the cost of their depression treatment decreases significantly after their depression is treated. This reduction partially offsets the cost of depression treatment over a follow-up period of 1 year. It is conceivable that the total costs of depression treatment are recovered over a longer time period, but long-term follow-up studies have not yet been carried out to determine whether this is the case.

EPIDEMIOLOGICAL STUDIES OF HELP SEEKING

Speed of Initial Treatment Contact

The findings reviewed above concerning the adverse effects of early-onset depression on role transitions raise an obvious question: Would timely treatment prevent these effects? We do not know the answer because the critical experiment has never been carried out. We do know, though, that timely treatment is the exception rather than the rule and that this is especially true for early-onset cases. This evidence comes from parallel studies of speed of initial treatment contact based on analysis of the NCS (Kessler, Olfson, & Berglund, 1998) and the Mental Health Supplement to the Ontario Health Survey (Olfson, Kessler, Berglund, & Lin, 1998). Both of these surveys asked respondents with a history of depression if they had ever sought treatment and, if so, their age of first obtaining treatment. Comparisons of reported ages of onset with ages of first obtaining treatment were used to study patterns and correlates of delay in seeking treatment. The results were consistent in the two surveys in showing that delays in initial help seeking are pervasive. Only about one-third of the people who ever sought treatment did so in the same years as the first onset of their MD, while the median delay among those who did not seek immediate treatment was more than 5 years. Even more striking was the consistent finding that speed of contact is strongly related to age of onset. The vast majority of respondents who reported first onsets of depression in middle age or later sought treatment soon after the onset. Respondents with first onsets in early adulthood, in comparison, were much slower to seek treatment. Respondents with child or adolescent onsets, finally, were by far the slowest of all, with median delays of more than a decade. It is not clear why this is the case, but one plausible hypothesis is that youngsters must rely on adults to initiate a treatment referral. Whatever the case may be, this is an especially disturbing pattern for two reasons. First, early-onset depression is often more severe than later-onset depression. Second, as noted above, early-onset depression has powerful effects on critical developmental transitions that affect well-being throughout life. These results strongly suggest that special efforts are needed to reach out to children and adolescents with depression

Current Service Use

Turning from speed of initial lifetime help-seeking to treatment at a point in time, data from two nationally representative epidemiological surveys in the United States show that between one-third and one-half of the people who meet criteria for MD in a given year obtain some type of treatment for their depression during that year (Kessler, Zhao, et al., 1999; Wang, Berglund, & Kessler, 2000). A substantial proportion of this treatment occurs in the general medical sector. Unfortunately, analysis of the content of this treatment in comparison to published treatment guidelines (Agency for Health Care Policy and Research, 1993; American Psychiatric Association, 1993) shows that no more than 30% of these patients receive even minimally acceptable treatment (Katz, Kessler, Lin, & Wells, 1998; Wang et al., 2000). There is clear evidence that depression treatment that fails to conform with treatment guidelines is associated with incomplete recovery and increased risk of recurrence (Melfi et al., 1998). These results show that advances in the development and implementation of treatment quality improvement programs are clearly needed.

Another development of great importance in depression treatment involves the rise of complementary and alternative (CAM) therapies. Three recently completed national surveys have documented that a substantial proportion of people with depression use a variety of CAM therapies, such as St. John's wort and relaxation therapy, to treat their depression

(Eisenberg et al., 1993; Eisenberg et al., 1998; Unutzer et al., 2000). In the most detailed of these surveys, which was carried out in 1997–1998, 54% of the respondents with self-defined "serious depression" in the year prior to the interview reported that they used some form of CAM for their depression (Kessler et al., 2001). An alternative medicine professional, such as an energy healer or herbalist, was seen during that same year for the treatment of depression by 19% of the respondents with self-defined serious depression. This compares to 36% who reported seeing any conventional physician or mental health professional for their depression during that same time period. The patients who used CAM were more likely to see a conventional provider than those who did not use CAM, with 66% of the patients who saw a conventional professional for their depression also using CAM.

Importantly, only a small minority of CAM users who are also in treatment with a conventional provider tell the latter about their CAM use (Eisenberg et al., 1998). It is important to recognize that this type of unsupervised joint use of CAM and conventional therapy can be dangerous, as case studies show that some types of CAM can create potentially dangerous interactions with pharmacotherapies (Yager, Siegfried, & DiMatteo, 1999; Almeida & Grimsley, 1996). For example, recent case reports suggest that the mixture of St. John's wort with selective serotonin reuptake inhibiters can induce a mild serotonin syndrome (Ernst, 1999). *In vitro* studies also suggest that hypericum extracts, which are commonly used herbal treatments for depression, are potent inducers of hepatic enzymes that can reduce plasma concentrations of a variety of concomitant prescription medications (Fugh-Berman, 2000). Opening up lines of communication between conventional mental health professionals and patients with regard to CAM use is consequently of great importance.

FUTURE DIRECTIONS

Developmental Epidemiology

There is an increased interest in developmental studies of the onset and course of depression as part of a larger interest in developmental epidemiology (Angold & Costello, 1995). The realization that first onset of depression often occurs early in life and that gender differences in depression begin to emerge in midadolescence are fueling this interest. It is likely that future developmental epidemiological studies will collect blood or saliva samples that can be used to measure sex hormones in an effort to tease out the biological and social effects of pubertal status and timing. Two epidemiological studies of adolescents have already collected data of this type and has shown that increases in sex hormones appear to explain much of the emerging sex difference in depression in midpuberty (Angold, Costello, & Worthman, 1998; Patton et al., 1996). It is also important, though, that these future studies give equal attention to social changes that occur at about the same time. The importance of this equal treatment is illustrated nicely in a recent report from the National Longitudinal Study of Adolescent Health (Bearman, Jones, & Udry, 1998), which showed that the greater increase in exposure to stresses associated with dating among girls than boys can explain much of the increasing sex difference in depression in midpuberty without reference to hormonal changes (Joyner & Udry, 2000).

Genetic Epidemiology

Psychiatric epidemiologists have been greatly interested in behavioral genetic studies of depression and other major mental disorders, with most of the focus being on twin and twin–family designs. Such studies use structural equation models to partition variances and

covariances into genetic and environmental components (Neale & Cardon, 1992). Although convincing data have been presented in these studies that depression is clearly heritable (Kendler et al., 1996), behavioral genetic studies have been disappointing in not advancing far beyond this basic fact. Some commentators on the future of psychiatric epidemiology have suggested that our greatest hope for a breakthrough in understanding the etiology of depression is likely to come from genetic epidemiology (Robins, 1992). However, there is no indication that this promise has begun to be fulfilled in the nearly two decades since epidemiological studies based on genetically informative designs (i.e., twin–family and adoption designs) have been actively pursued. Linkage studies have been unable to identify a single specific gene or gene marker for any mood disorder. If such markers can be identified, integration of psychiatric epidemiology with population genetics would be valuable in a number of ways (Risch & Merikangas, 1996). It is not clear, though, when and if such markers will be identified.

Experimental Epidemiology

Epidemiology has played a major part in the development of many public health interventions. Important epidemiological contributions along these same lines are beginning to emerge in psychiatric epidemiology as well. Included here are studies that have documented effects of obstetrical complications on childhood-onset schizophrenia (Nicholson et al., 1999), of childhood nutritional deficits on conduct disorder (Neugebauer, Hoek, & Susser, 1999), and of childhood lead exposure on early-onset Alzheimer's disease (Prince, 1998). However, the enormous complexity of environmental etiological processes in bringing about mental disorders has led most psychiatric epidemiologists to focus their efforts on broad nonspecific risk factors such as stress, social support, social class, and gender that do not have clear intervention implications. As a result, psychiatric epidemiologists have been less actively involved in targeting interventions than epidemiologists working in other areas of research. (For an important exception, see Harris, Brown, & Robinson, 1999a, 1999b.) As described in more detail elsewhere (Kessler, 2000b), the way in which analytic epidemiological research is carried out differs in important ways depending on whether the researcher sees the work as important for hypothesis testing or for guiding intervention development and targeting. If future psychiatric epidemiologists are to become closely involved in intervention work, changes will be needed in the types of questions asked, the kinds of analyses carried out, and the standards of proof required for epidemiological studies.

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REFERENCES

Agency for Health Care Policy and Research. (1993). *Treatment of major depression: Vol. 2. Depression in primary care*. Rockville, MD: U.S. Department of Health and Human Services.

Akiskal, H. S. (1990). Toward a clinical understanding of the relationship of anxiety and depressive disorders. In J. D. Maser & C. R. Cloninger (Eds.), *Comorbidity of mood and anxiety disorders* (pp. 597–607). Washington, DC: American Psychiatric Press.

Almeida, J. C., & Grimsley, E. W. (1996). Coma from the health food store: Interaction between kava and alprazolam [letter]. *Annals of Internal Medicine*, *125*(11), 940–941.

American Psychiatric Association. (1980). *Diagnostic and statistical manual of mental disorders* (3rd ed.). Washington, DC: Author.

American Psychiatric Association. (1987). *Diagnostic and statistical manual of mental disorders* (3rd ed., rev.). Washington, DC: Author.

American Psychiatric Association. (1993). Practice guideline for major depressive disorder in adults. *American Journal of Psychiatry*, *150*(4, Suppl.), 1–26.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.). Washington, DC: Author.

Angold, A., & Costello, E. J. (1995). Developmental epidemiology. *Epidemiologic Reviews*, *17*(1), 74–82.

Angold, A., Costello, E. J., & Worthman, C. M. (1998). Puberty and depression: The roles of age, pubertal status and pubertal timing. *Psychological Medicine*, *28*(1), 51–61.

Angst, J., & Merikangas, K. (1997). The depressive spectrum: Diagnostic classification and course. *Journal of Affective Disorders*, *45*(1–2), 31–39; discussion, 39–40.

Angst, J., Sellaro, R., & Merikangas, K. R. (2000). Depressive spectrum diagnoses. *Comprehensive Psychiatry*, *41*(2, Suppl. 1), 39–47.

Bearman, P., Jones, J., & Udry, J. R. (1998). *The National Longitudinal Study of Adolescent Health: Research design.* Chapel Hill, NC: Carolina Population Center.

Bland, R.C. (1997). Epidemiology of affective disorders: a review. *Canadian Journal of Psychiatry, 42*(4), 367–377.

Blazer, D. G. (2000). Mood disorders: Epidemiology. In B. J. Sadock & V. A. Sadock (Eds.), *Kaplan and Sadock's comprehensive textbook of psychiatry* (7th ed., pp. 1298–1308). Philadelphia: Lippincott Williams & Wilkins.

Blazer, D. G., Kessler, R. C., & Swartz, M. S. (1998). Epidemiology of recurrent major and minor depression with a seasonal pattern: The National Comorbidity Survey. *British Journal of Psychiatry*, *172*, 164–167.

Booker, J. M., & Hellekson, C. J. (1992). Prevalence of seasonal affective disorder in Alaska. *American Journal of Psychiatry*, *149*(9), 1176–1182.

Bradburn, N., Sudman, S., & Associates (1979). *Improving interview method and questionnaire design: Response effects to threatening questions in survey research*. San Francisco: Jossey-Bass.

Brugha, T. S., Bebbington, P. E., MacCarthy, B., Sturt, E., Wykes, T., & Potter, J. (1990). Gender, social support and recovery from depressive disorders: A prospective clinical study. *Psychological Medicine*, *20*, 147–156.

Christie, K. A., Burke, J. D., Jr., Regier, D. A., Rae, D. S., Boyd, J. H., & Locke, B. Z. (1988). Epidemiologic evidence for early onset of mental disorders and higher risk of drug abuse in young adults. *American Journal of Psychiatry, 145*(8), 971–975.

Cloninger, C. R. (1989). Establishment of diagnostic validity in psychiatric illness: Robins and Guze's method revised. In L. N. Robins & J. Barrett (Eds.), *Validity of psychiatric diagnosis* (pp. 9–18). New York: Raven Press.

Danziger, S. K., Corcoran, M., Danziger, S., Heflin, C., Kalil, A., Levine, J., Rosen, D., Seefeldt, K., Siefert, K., & Tolman, R. (2000). Barriers to the employment of welfare recipients. In R. Cherry & W. Rodgers (Eds.), *Prosperity for all?: The economic boom and African Americans* (pp. 245–278). New York: Russell Sage Foundation.

Davidson, J., Woodbury, M. A., Pelton, S., & Krishnan, R. (1988). A study of depressive typologies using grade of membership analysis. *Psychological Medicine*, *18*(1), 179–189.

Derogatis, L. R. (1977). *SCL-90 administration, scoring and procedures manual for the revised version*. Baltimore: Johns Hopkins University Press.

Eaton, J. W., & Weil, R. J. (1955). *Culture and mental disorders*. Glencoe, IL: Free Press.

Eaton, W. W., Dryman, A., Sorenson, A., & McCutcheon, A. (1989). DSM-III major depressive disorder in the community: A latent class analysis of data from the NIMH Epidemiologic Catchment Area programme. *British Journal of Psychiatry*, *155*, 48–54.

Eisenberg, D., Davis, R. B., Ettner, S. L., Appel, S., Wilkey, S., van Rompay, M., & Kessler, R. C.

(1998). Trends in alternative medicine use in the United States, 1990–1997: Results of a follow-up national survey. *Journal of the American Medical Association*, *280*, 1569–1575.

Eisenberg, D. M., Kessler, R. C., Foster, C., Norlock, F. E., Calkins, D. R., & Delbanco, T. L. (1993). Unconventional medicine in the United States: Prevalence, costs, and patterns of use. *New England Journal of Medicine*, *328*(4), 246–252.

Ernst, E. (1999). Second thoughts about safety of St. John's wort. *Lancet*, *354*(9195), 2014–2016.

Faris, R., & Dunham, H. (1939). *Mental disorders in urban areas*. Chicago: University of Chicago Press.

First, M. B., Spitzer, R. L., & Williams, J. B. W. (1990). Exclusionary principles and the comorbidity of psychiatric diagnoses: A historical review and implications for the future. In J. D. Maser & C. R. Cloninger (Eds.), *Comorbidity of mood and anxiety disorders* (pp. 83–109). Washington, DC: American Psychiatric Press.

Frances, A., Manning, D., Marin, D., Kocsis, J., McKinney, K., Hall, W., & Kline, M. (1992). Relationship of anxiety and depression. *Psychopharmacology*, *106*, S82–S86.

Freeman, E. W., DeRubeis, R. J., & Rickels, K. (1996). Reliability and validity of a daily diary for premenstrual syndrome. *Psychiatry Research*, *65*(2), 97–106.

Freeman, E. W., Rickels, K., Sondheimer, S. J., & Polansky, M. (1999). Differential response to antidepressants in women with premenstrual syndrome/premenstrual dysphoric disorder: A randomized controlled trial. *Archives of General Psychiatry*, *56*(10), 932–939.

Fugh-Berman, A. (2000). Herb–drug interactions. *Lancet*, *355*(9198), 134–138.

Ghaziuddin, M., Ghaziuddin, N., & Stein, G. S. (1990). Life events and the recurrence of depression. *Canadian Journal of Psychiatry*, *35*(3), 239–242.

Giuffra, L. A., & Risch, N. (1994). Diminished recall and the cohort effect of major depression: A stimulation study. *Psychological Medicine*, *24*, 375–383.

Gold, M. R., Siegel, J. E., Russell, L. B., & Weinstein, M. C. (1996). *Cost-effectiveness in health and medicine*. New York: Oxford University Press.

Goldberg, D. P. (1972). *The detection of psychiatric illness by questionnaire: A technique for the identification and assessment of non-psychotic psychiatric illness*. London: Oxford University Press.

Gotlib, I. H., Lewinsohn, P. M., & Seeley, J. R. (1995). Symptoms versus a diagnosis of depression: Differences in psychosocial functioning. *Journal of Consulting and Clinical Psychology*, *63*(1), 90–100.

Greenberg, P., Kessler, R., Nells, T., Finkelstein, S., & Berndt, E. R. (1996). Depression in the workplace: An economic perspective. In J. P. Feighner & W. F. Boyer (Eds.), *Selective serotonin reuptake inhibitors: Advances in basic research and clinical practice* (pp. 327–363). New York: Wiley.

Halbreich, U. (1997). Premenstrual dysphoric disorders: A diversified cluster of vulnerability traits to depression. *Acta Psychiatrica Scandinavica*, *95*(3), 169–176.

Hammen, C., & Gitlin, M. (1997). Stress reactivity in bipolar patients and its relation to prior history of disorder. *American Journal of Psychiatry, 154*(6), 856–857.

Harris, T., Brown, G. W., & Robinson, R. (1999a). Befriending as an intervention for chronic depression among women in an inner city: 1. Randomised controlled trial. *British Journal of Psychiatry*, *174*, 219–224.

Harris, T., Brown, G. W., & Robinson, R. (1999b). Befriending as an intervention for chronic depression among women in an inner city: 2. Role of fresh-start experiences and baseline psychosocial factors in remission from depression. *British Journal of Psychiatry*, *174,* 225–232.

Horwath, E., & Weissman, M. M. (1995). Epidemiology of depression and anxiety disorders. In M. T. Tsuang, M. Tohen, & G. E. P. Zahner (Eds.), *Textbook in psychiatric epidemiology* (pp. 317–344). New York: Wiley.

Joyner, K., & Udry, J. R. (2000). You don't bring me anything but down: Adolescent romance and depression. *Journal of Health and Social Behavior*, *41*(4), 369–391.

Judd, L. L., Akiskal, H. S., & Paulus, M. P. (1997). The role and clinical significance of subsyndromal depressive symptoms (SSD) in unipolar major depressive disorder. *Journal of Affective Disorders*, *45*(1–2), 5–17; discussion, 17–18.

Katon, W., Robinson, P., Von Korff, M., Lin, E., Bush, T., Ludman, E., Simon, G., & Walker, E.

(1996). A multifaceted intervention to improve treatment of depression in primary care. *Archives of General Psychiatry*, *53*(10), 924–932.

Katz, S. J., Kessler, R. C., Lin, E., & Wells, K. B. (1998). Medication management of depression in the United States and Ontario. *Journal of General Internal Medicine*, *13*(2), 77–85.

Katzelnick, D. J., Simon, G. E., Pearson, S. D., Manning, W. G., Helstad, C. P., Henk, H. J., Cole, S. M., Lin, E. H., Taylor, L. H., & Kobak, K. A. (2000). Randomized trial of a depression management program in high utilizers of medical care. *Archives of Family Medicine*, *9*(4), 345–351.

Kendell, R. E. (1976). The classification of depressions: A review of contemporary confusion. *British Journal of Psychiatry*, *129*, 15–28.

Kendler, K. S., Eaves, L. J., Walters, E. E., Neale, M. C., Heath, A. C., & Kessler, R. C. (1996). The identification and validation of distinct depressive syndromes in a population-based sample of female twins. *Archives of General Psychiatry, 53*, 391–399.

Kendler, K. S., Walters, E. E., & Kessler, R. C. (1997). The prediction of length of major depressive episodes: Results from an epidemiological sample of female twins. *Psychological Medicine*, *27*(1), 107–117.

Kessler, R. C. (1995). The epidemiology of psychiatric comorbidity. In M. T. Tsaung, M. Tohen, & G. E. P. Zahner (Eds.), *Textbook in psychiatric epidemiology* (pp. 179–197). New York: Wiley.

Kessler, R. C. (1997a). The effects of stressful life events on depression. *Annual Review of Psychology, 48,* 191–214.

Kessler, R. C. (1997b). The prevalence of psychiatric comorbidity. In S. Wetzler & W. C. Sanderson (Eds.), *Treatment strategies for patients with psychiatric comorbidity* (pp. 23–48). New York: Wiley.

Kessler, R. C. (2000a). Gender difference in major depression: Epidemiological findings. In E. Frank (Ed.), *Gender and its effect in psychopathology* (pp. 61–84). Washington, DC: American Psychiatric Press.

Kessler, R. C. (2000b). Psychiatric epidemiology: Selected recent advances and future directions. *Bulletin of the World Health Organization*, *78*(4), 464–474.

Kessler, R. C. (2000c). Burden of depression. In S. Kasper & A. Carlsson (Eds.), *Selective serotonin reuptake inhibitors 1990–2000: A decade of developments.* Copenhagen, Denmark: H. Lundbeck A/S.

Kessler, R. C., Avenevoli, S., & Merikangas, S. K. (2001). Mood disorders in children and adolescents: An epidemiological perspective. *Biological Psychiatry, 49,* 1002–1014.

Kessler, R. C., Barber, C., Birnbaum, H. G., Frank, R. G., Greenberg, P. E., Rose, R. M., Simon, G. E., & Wang, P. (1999). Depression in the workplace: Effects on short-term disability. *Health Affairs*, *18*(5), 163–171.

Kessler, R. C., Berglund, P. A., Foster, C. L., Saunders, W. B., Stang, P. E., & Walters, E. E. (1997). Social consequences of psychiatric disorders: II. Teenage parenthood. *American Journal of Psychiatry*, *154*(10), 1405–1411.

Kessler, R. C., Foster, C. L., Saunders, W. B., & Stang, P. E. (1995). Social consequences of psychiatric disorders: I. Educational attainment. *American Journal of Psychiatry*, *152*(7), 1026–1032.

Kessler, R. C., Foster, C., Webster, P. S., & House, J. S. (1992). The relationship between age and depressive symptoms in two national surveys. *Psychology and Aging*, *7*(1), 119–126.

Kessler, R. C., & Frank, R. G. (1997). The impact of psychiatric disorders on work loss days. *Psychological Medicine*, *27*(4), 861–873.

Kessler, R. C., & Magee, W. J. (1993). Childhood adversities and adult depression: Basic patterns of association in a U.S. national survey. *Psychological Medicine*, *23*, 679–690.

Kessler, R. C., McGonagle, K. A., Swartz, M., Blazer, D. G., & Nelson, C. B. (1993). Sex and depression in the National Comorbidity Survey: I. Lifetime prevalence, chronicity and recurrence. *Journal of Affective Disorders*, *29*(2–3), 85–96.

Kessler, R. C., McGonagle, K. A., Zhao, S., Nelson, C. B., Hughes, M., Eshleman, S., Wittchen, H.-U., & Kendler, K. S. (1994). Lifetime and 12–month prevalence of DSM-III-R psychiatric disorders in the United States: Results from the National Comorbidity Survey. *Archives of General Psychiatry*, *51*, 8–19.

Kessler, R. C., Mickelson, K. D., Barber, C. B., & Wang, P. (2001). The association between chronic

medical conditions and work impairment. In A. S. Rossi (Ed.), *Caring and doing for others: Social responsibility in the domains of the family, work, and community* (pp. 403–426). Chicago: University of Chicago Press.

Kessler, R. C., Nelson, C. B., McGonagle, K. A., Liu, J., Swartz, M. S., & Blazer, D. G. (1996). Comorbidity of DSM-III-R major depressive disorder in the general population: Results from the U.S. National Comorbidity Survey. *British Journal of Psychiatry*, *168*, 17–30.

Kessler, R. C., Olfson, M., & Berglund, P. A. (1998). Patterns and predictors of treatment contact after first onset of psychiatric disorders. *American Journal of Psychiatry*, *155*(1), 62–69.

Kessler, R. C., Soukup, J., Davis, R. B., Foster, D. F., Wilkey, S. A., Van Rompay, M. I., & Eisenberg, D. M. (2001). The use of complementary and alternative therapies to treat anxiety and depression in the United States. *American Journal of Psychiatry, 158*(2), 289–294.

Kessler, R. C., & Ustun, T. B. (2000). The World Health Organization World Mental Health 2000 (WMH2000) initiative: Editorial. *Hospital Management International.*

Kessler, R. C., & Walters, E. E. (1998). Epidemiology of DSM-III-R major depression and minor depression among adolescents and young adults in the National Comorbidity Survey. *Depression and Anxiety, 7*, 3–14.

Kessler, R. C., Walters, E. E., & Forthofer, M. S. (1998). The social consequences of psychiatric disorders. III. Probability of marital stability. *American Journal of Psychiatry*, *155*(8), 1092–1096.

Kessler, R. C., Wittchen, H.-U., Abelson, J., Kendler, K., Knauper, B., McGonagle, K. M., Schwarz, N., & Zhao, S. (1998). Methodological studies of the Composite International Diagnostic Interview (CIDI) in the U.S. National Comorbidity Survey. *International Journal of Methods in Psychiatric Research*, *7*, 33–55.

Kessler, R. C., Wittchen, H.-U., Abelson, J., & Zhao, S. (2000). Methodological issues in assessing psychiatric disorder with self-reports. In A. A. Stone, J. S. Turrkan, C. A. Bachrach, J. B. Jobe, H. S. Kurtzman, & V. S. Cain (Eds.), *The science of self-report: Implications for research and practice* (pp. 229–255). Mahwah, NJ: Erlbaum.

Kessler, R. C., Zhao, S., Blazer, D. G., & Swartz, M. (1997). Prevalence, correlates and course of minor depression and major depression in the National Comorbidity Study. *Journal of Affective Disorders, 45*(1–2), 19–30.

Kessler, R. C., Zhao, S., Katz, S. J., Kouzis, A. C., Frank, R. G., Edlund, M., & Leaf, P. (1999). Past year use of outpatient services for psychiatric problems in the National Comorbidity Survey. *American Journal of Psychiatry*, *156*, 115–123.

Leighton, D. C., Harding, J. S., & Macklin, D. B. (1963). *Stirling County Study: Vol. 3. The character of danger.* New York: Basic Books.

Lewinsohn, P. M., Allen, N. B., Seeley, J. R., & Gotlib, I. H. (1999). First onset versus recurrence of depression: Differential processes of psychosocial risk. *Journal of Abnormal Psychology, 108*(3), 483–489.

Lewinsohn, P. M., Rohde, P., Seeley, J. R., & Fischer, S. A. (1991). Age and depression: Unique and shared effects. *Psychology and Aging*, *6*(2), 247–260.

Lewinsohn, P. M., Rohde, P., Seeley, J. R., Klein, D. N., & Gotlib, I. H. (2000). Natural course of adolescent major depressive disorder in a community sample: Predictors of recurrence in young adults. *American Journal of Psychiatry*, *157*(10), 1584–1591.

Link, B. G., & Dohrenwend, B. P. (1980). Formulation of hypotheses about the true relevance of demoralization in the United States. In B. P. Dohrenwend, B. S. Dohrenwend, M. Schwarz-Gould, B. Link, R. Neugebauer, & R. Wunsch-Hitzig (Eds.), *Mental illness in the United States: Epidemiological estimates* (pp. 114–132). New York: Praeger.

McLeod, J. D., Kessler, R. C., & Landis, K. R. (1992). Speed of recovery from major depressive episodes in a community sample of married men and women. *Journal of Abnormal Psychology*, *101*(2), 277–286.

Melfi, C. A., Chawla, A. J., Croghan, T. W., Hanna, M. P., Kennedy, S., & Sredl, K. (1998). The effects of adherence to antidepressant treatment guidelines on relapse and recurrence of depression. *Archives of General Psychiatry*, *55*(12), 1128–1132.

Merikangas, K. R. (2000). Epidemiology of mood disorders in women. In M. Steiner, K. A. Yonkers, & E. Eriksson (Eds.), *Mood disorders in women* (pp. 1–14). London: Martin Dunitz.

Merikangas, K. R., & Angst, J. (1995). The challenge of depressive disorders in adolescence. In M. Rutter (Ed.), *Psychosocial disturbances in young people: Challenges for prevention* (pp. 131–165). Cambridge, UK: Cambridge University Press.

Mintz, J., Mintz, L. I., Arruda, M. J., & Hwang, S. S. (1992). Treatments of depression and the functional capacity to work. *Archives of General Psychiatry*, *49*(10), 761–768.

Murphy, J. M., Laird, N. M., Monson, R. R., Sobol, A. M., & Leighton, A. H. (2000). A 40–year perspective on the prevalence of depression: The Stirling County Study. *Archives of General Psychiatry, 57*(3), 209–215.

Murray, C. J. L., & Lopez, A. D. (Eds.). (1996). *The global burden of disease: A comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020.* Cambridge, MA: Harvard University Press.

Neale, M. C., & Cardon, L. R. (1992). *Methodology for genetic studies of twins and families*. Dordrecht, The Netherlands: Kluwer Academic Press.

Neugebauer, R., Hoek, H. W., & Susser, E. (1999). Prenatal exposure to wartime famine and development of antisocial personality disorder in early adulthood. *Journal of the American Medical Association*, *282*(5), 455–462.

Nicolson, R., Malaspina, D., Giedd, J. N., Hamburger, S., Lenane, M., Bedwell, J., Fernandez, T., Berman, A., Susser, E., & Rapoport, J. L. (1999). Obstetrical complications and childhood-onset schizophrenia. *American Journal of Psychiatry*, *156*(10), 1650–1652.

Offord, D. R., Boyle, M., Campbell, D., Cochrane, J., Goering, P. N., Lin, E., Rhodes, A., & Wong, M. (1994). *Mental health in Ontario: Selected findings from the Mental Health Supplement to the Ontario Health Survey*. Toronto: Queen's Printer for Ontario.

Olfson, M., Kessler, R. C., Berglund, P. A., & Lin, E. (1998). Psychiatric disorder onset and first treatment contact in the United States and Ontario. *American Journal of Psychiatry*, *155*(10), 1415–1422.

Olive, D. L. (1991). The prevalence and epidemiology of luteal-phase deficiency in normal and infertile women. *Clinical Obstetrics and Gynecology*, *34*(1), 157–166.

Olson, K., & Pavetti, L. (1996). *Personal and family challenges to the successful transition from welfare to work*. Washington, DC: Urban Institute.

Patton, G. C., Hibbert, M. E., Carlin, J., Shao, Q., Rosier, M., Caust, J., & Bowes, G. (1996). Menarche and the onset of depression and anxiety in Victoria, Australia. *Journal of Epidemiology and Community Health, 50*(6), 661–666.

Pearlstein, T., & Stone, A. B. (1998). Premenstrual syndrome. *Psychiatric Clinics of North America*, *21*(3), 577–590.

Prince, M. (1998). Is chronic low-level lead exposure in early life an etiologic factor in Alzheimer's disease? *Epidemiology*, *9*(6), 618–621.

Regier, D. A., Kaelber, C. T., Rae, D. S., Farmer, M. E., Knauper, B., Kessler, R. C., & Norquist, G. S. (1998). Limitations of diagnostic criteria and assessment instruments for mental disorders: Implications for research and policy. *Archives of General Psychiatry*, *55*(2), 109–115.

Regier, D. A., Narrow, W. E., Rupp, A., Rae, D. S., & Kaelber, C. T. (2000). The epidemiology of mental disorder treatment need: Community estimates of "medical necessity." In G. Andrews & S. Henderson (Eds.), *Unmet need in psychiatry: Problems, resources, responses* (pp. 41–58). Cambridge, UK: Cambridge University Press.

Risch, N., & Merikangas, K. R. (1996). The future of genetic studies of complex human diseases. *Science*, *273*, 1516–1517.

Robins, L. N. (1992). The future of psychiatric epidemiology. *International Journal of Methods in Psychiatric Research*, *2*, 1–3.

Robins, L. N., Helzer, J. E., Croughan, J., Williams, J. B. W., & Spitzer, R. L. (1981). *NIMH Diagnostic Interview Schedule: Version III*. Rockville, MD: National Institute of Mental Health.

Robins, L. N., Locke, B. Z., & Regier, D. A. (1991). An overview of psychiatric disorders in America. In L. N. Robins & D. A. Regier (Eds.), *Psychiatric disorders in America: The Epidemiologic Catchment Area Study* (pp. 328–366). New York: Free Press.

Robins, L. N., & Regier, D. A. (Eds.). (1991). *Psychiatric disorders in America: The Epidemiologic Catchment Area Study*. New York: Free Press.

Robins, L. N., Wing, J., Wittchen, H. U., Helzer, J. E., Babor, T. F., Burke, J., Farmer, A., Jablenski, A., Pickens, R., Regier, D. A., et al. (1988). The Composite International Diagnostic Interview: An epidemiologic instrument suitable for use in conjunction with different diagnostic systems and in different cultures. *Archives of General Psychiatry*, *45*(12), 1069–1077.

Rosen, L. N., Targum, S. D., Terman, M., Bryant, M. J., Hoffman, H., Kasper, S. F., Hamovit, J. R., Docherty, J. P., Welch, B., & Rosenthal, N. E. (1990). Prevalence of seasonal affective disorder at four latitudes. *Psychiatry Research*, *31*(2), 131–144.

Rosenthal, N. E., Sack, D. A., Gillin, J. C., Lewy, A. J., Goodwin, F. K., Davenport, Y., Mueller, P. S., Newsome, D. A., & Wehr, T. A. (1984). Seasonal affective disorder: A description of the syndrome and preliminary findings with light therapy. *Archives of General Psychiatry*, *41*(1), 72–80.

Seiler, L. H. (1973). The 22–item scale used in field studies of mental illness: A question of method, a question of substance, and a question of theory. *Journal of Health and Social Behavior*, *14*(3), 252–264.

Severino, S. K. (1996). Premenstrual dysphoric disorder: Controversies surrounding the diagnosis. *Harvard Review of Psychiatry*, *3*(5), 293–295.

Sheehan, D., Lecrubier, Y., Sheehan, K., Amorim, P., & Janavs, J. (1998). The Mini-International Neuropsychiatric Interview (MINI): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry*, *59*(Suppl. 20), 22–33.

Spitzer, R. L., Williams, J. B., Kroenke, K., Linzer, M., deGruy, F. V., 3rd, Hahn, S. R., Brody, D., & Johnson, J. G. (1994). Utility of a new procedure for diagnosing mental disorders in primary care: The PRIME-MD 1000 study. *Journal of the American Medical Association, 272*(22), 1749–1756.

Srole, L., Langner, T. S., Michael, S. T., Opler, M. K., & Rennie, T. A. C. (1962). *Mental health in the metropolis: The Midtown Study*. New York: McGraw-Hill.

Sullivan, P. F., Kessler, R. C., & Kendler, K. S. (1998). Latent class analysis of lifetime depressive symptoms in the National Comorbidity Survey. *American Journal of Psychiatry*, *155*(10), 1398–1406.

Sveindottir, H., & Backstrom, T. (2000). Prevalence of menstrual cycle symptom cyclicity and premenstrual dysphoric disorder in a random sample of women using and not using oral contraceptives. *Acta Obstetrica et Gynecologica Scandinavica*, *79*(5), 405–413.

Turner, C. F., & Martin, E. (1984). *Surveying subjective phenomena* (Vol. I). New York: Russell Sage Foundation.

Unutzer, J., Klap, R., Sturm, R., Young, A. S., Marmon, T., Shatkin, J., & Wells, K. B. (2000). Mental disorders and the use of alternative medicine: Results from a national survey. *American Journal of Psychiatry*, *157*(11), 1851–1857.

Vega, W. A., Kolody, B., Aguilar-Gaxiola, S., Alderete, E., Catalano, R., & Caraveo-Anduaga, J. (1998). Lifetime prevalence of DSM-III-R psychiatric disorders among urban and rural Mexican Americans in California. *Archives of General Psychiatry*, *55*(9), 771–778.

Wang, P. S., Berglund, P., & Kessler, R. C. (2000). Recent care of common mental disorders in the United States: Prevalence and conformance with evidence-based recommendations. *Journal of General Internal Medicine*, *15*(5), 284–292.

Weissman, M. M., Bruce, M. L., Leaf, P. J., Florio, L. P., & Holzer, C. III. (1991). Affective disorders. In L. N. Robins & D. A. Regier (Eds.), *Psychiatric disorders in America* (pp. 53–80). New York: Free Press.

Weissman, M. M., & Klerman, G. L. (1992). Depression: Current understanding and changing trends. *Annual Review of Public Health*, *13*, 319–339.

Wells, K. B., Sherbourne, C., Schoenbaum, M., Duan, N., Meredith, L., Unutzer, J., Miranda, J., Carney, M. F., & Rubenstein, L. V. (2000). Impact of disseminating quality improvement programs for depression in managed primary care: A randomized controlled trial. *Journal of the American Medical Association*, *283*(2), 212–220.

Wells, K., Stewart, A., Hays, R., Burnam, M., Rogers, W., Daniels, M., Berry, S., Greenfield, S., & Ware, J. (1989). The functioning and well-being of depressed patients: Results from the Medical Outcomes Study. *Journal of the American Medical Association*, *262*, 914–919.

WHO International Consortium in Psychiatric Epidemiology. (2000). Cross-national comparisons of the prevalences and correlates of mental disorders. *Bulletin of the World Health Organization*, *78*(4), 413–426.

Yager, J., Siegfreid, S. L., & DiMatteo, T. L. (1999). Use of alternative remedies by psychiatric patients: Illustrative vignettes and a discussion of the issues. *American Journal of Psychiatry*, *156*(9), 1432–1438.

Yonkers, K. A. (1997). The association between premenstrual dysphoric disorder and other mood disorders. *Journal of Clinical Psychiatry*, *58*(Suppl. 15), 19–25.