RISK FACTORS FOR MAJOR DEPRESSION AND BIPOLAR DISORDER

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Epidemiology is the study of the distribution of diseases and disorders in human populations and the variation in these distributions in different population subgroups. An observation that a disease is higher in one group or another helps to identify risk factors or correlates of these high rates whose alteration will interrupt the causal sequence that produces the disorder. Epidemiologic methods have been grouped into descriptive studies, which provide basic estimates of rates and their variation or increased risk in a population; analytic studies, which explore the variations in rates among different groups and identify risk factors; and experimental studies, which test an association between a risk factor and a disorder and seek to control or reduce the occurrence by controlling the risk factor.

Epidemiologic methods used in psychiatry are identical to those used in other branches of medicine. In psychiatry there are few clearly defined and modifiable risk factors, so studies have focused on largely unmodifiable ones such as age and gender, although even these risk factors can be useful in providing a clue to etiology.

The evidence of risk factors for depression came primarily from descriptive (large-scale epidemiologic) studies and analytic (family and high-risk offspring) studies. The former is useful as a first step because the samples include subjects regardless of treatment and thus are unbiased. The latter are useful as they include control groups and can be used to calculate relative risks.

This chapter reviews the current evidence for risk factors associated with major depression (MD) and bipolar disorder primarily based on cross-national community surveys and some family studies.

MAJOR DEPRESSION

Prevalence

Data on prevalence of unipolar MD based on epidemiologic community surveys using the same diagnostic assessment, the Diagnostic Interview Schedule (DIS), are now available from different parts of the world. These population-based epidemiologic studies were conducted in the 1980s, and a cross-national collaboration was formed to analyze the data together in a standardized way. Ten countries across the world, including North America, Europe, Asia, and New Zealand, participated. These data provide the first information on cross-national rates for risk factors using the same methods. The lifetime prevalence rates of MD range from 1.5 per 100 adults in Taiwan to 19.0 per 100 in Lebanon. The results showed considerable variation in rates, but consistency in sex differences and age of onset.

In the United States, the National Institute of Mental Health (NIMH) Epidemiologic Catchment Area (ECA) study conducted in 1980 reported an overall lifetime prevalence of 5.2 per 100 and a 1-year prevalence of 3.0 per 100, which was somewhat lower than the rate reported by other studies across the world (1). In the National Comorbidity Survey (NCS) conducted a decade later in the United States, a substantially higher lifetime prevalence of MD was reported—17.1 (2). All prevalence rates have been published individually, but for the purpose of comparison between the countries they have been standardized to the U.S. age and sex distribution (Table 70.1).

The disparity between the rates reported in the ECA and the NCS has generated considerable controversy and discussion. Whether the differences are real (reflecting a substantial change in the prevalence rate over the decade) or artifactual (due to differences in methodology) has prompted careful examination. It is now believed that the difference is due to methodology (e.g., different diagnostic assessment, sample age, and size), and not to a true increase in the rate over the decade.

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2.9

11.6

Country	Lifetime Rate/100				
	Overall	Females	Males	F/M Ratio	Mean Age at Onset
United States (ECA, 1980)	5.2	7.4	2.8	2.6	25.6
United States (NCS, 1990)	17.1	21.3	12.7	1.7	23.8
Canada	9.6	12.3	6.8	1.9	24.8
Puerto Rico	4.3	5.5	3.1	1.8	29.5
France	16.4	21.9	10.5	2.1	29.2
Germany	9.2	13.5	4.4	3.1	29.7
Italy	12.4	18.1	6.1	3.0	34.8
Lebanon	19.0	23.1	14.7	1.6	25.2
Taiwan (Taipei)	1.5	1.8	1.1	1.6	29.3

TABLE 70.1. CROSS-NATIONAL LIFETIME PREVALENCE OF MAJOR DEPRESSION^a

CIDI, Composite International Diagnostic Interview; DIS, Diagnostic Interview Schedule; ECA, Epidemiologic Catchment Area Study; NCS, National Comorbidity Survey.

^aRates have been standardized to the U.S. age and sex distribution (adapted from ref. 1). All studies used the DIS with the exception of the NCS, which used the CIDI.

1.9

7.5

2.0

2.1

3.8

15.5

Gender

Despite the variation in rates, the most consistent finding in the cross-national studies and the two U.S. studies is the increased rate of MD in women (Table 70.1). The reasons for this disparity are not clear, but the disparity is also found in clinical studies. Interestingly, prior to puberty there are no sex differences in rates of depression. However, following puberty there is a dramatic shift in the prevalence rates, with a twofold increase in the prevalence of depression among women compared to men. A higher risk of depression in women is probably accounted for primarily by the higher risk of first onset in women. A series of analyses of the NCS data shows that there is little difference in the probability of acute recurrence in women and in men with a history of depression (3). Many theories, biological, psychosocial, and artifactual, attempt to explain this dramatic increase in the prevalence of depression among women, but none is fully satisfactory.

Korea (Seoul)

New Zealand

Age Of Onset And Secular Changes

The age of first onset of MD is fairly consistent across studies (Table 70.1). Of the ten major population-based epidemiologic studies reported by Weissman et al. (1), eight reported the age of onset between 25 and 30 years. In the NCS, the age of onset was 24 (3). Although there is consistency across studies regarding the age of onset, there is some evidence that the age of onset of depression has decreased over the last half century (4). In 1985, using the data from the NIMH Collaborative Program on the Psychobiology of Depression, the cumulative probability of a first episode of

MD in female relatives of patients with MD by age 30 was less than 10% in individuals born before 1929. This rate doubled in cohorts born between 1930 and 1949, and among those born after 1950 the rate skyrocketed to 60%. The rate in males also increased in younger cohorts, but not nearly as dramatically as in women (Figs. 70.1 and 70.2).

29.3

27.3

An analysis of the ECA data by Wickramaratne and colleagues (5) showed an increase in the rate of MD in the cohort born between 1935 and 1945. The rates for females stabilized after this increase. However, rates for males continued to rise in the cohort born between 1945 and 1954, and then decreased in the most recent cohort of the study,

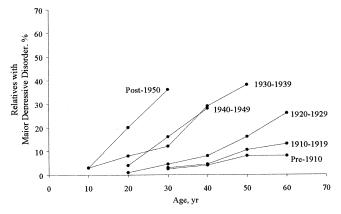


FIGURE 70.1. Cumulative probability of diagnosable major depressive disorder in male relatives by birth cohort. (Adapted from Klerman GL, Lavori PW, Rice J, et al. Birth-cohort trends in rates of major depressive disorder among relatives of patients with affective disorder. *Arch Gen Psychiatry* 1985;42(7):689–693.)

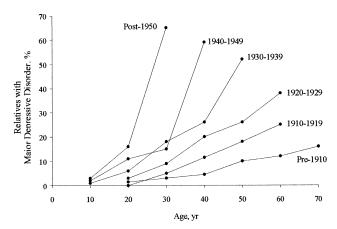


FIGURE 70.2. Cumulative probability of diagnosable major depressive disorder in female relatives by birth cohort. (Adapted from Klerman GL, Lavori PW, Rice J, et al. Birth-cohort trends in rates of major depressive disorder among relatives of patients with affective disorder. *Arch Gen Psychiatry* 1985;42(7):689–693.)

those born between 1955 and 1964. In the NCS (2), lifetime risk of MD increased consistently through increasingly younger cohorts. In the youngest cohort (born between 1966 and 1975) there was a substantial increase in the risk of first onset in early adulthood compared to all other cohorts. The finding was true for both men and women.

With regard to prevalence across adulthood in the NCS, 30-day prevalence was fairly constant between the ages of 15 and 44, but dropped by nearly half in the decade between 45 and 54. As has already been mentioned, among women the prevalence was very high, 8.2% in the 15 to 24 cohort,

and then dropped off to between 4% and 6% in subsequent decades, without a reduction as they age (6).

Marital Status

Marital status has been found to be highly associated with onset and prevalence of depression, but not with treatment outcome. In the ECA and the NCS, married and nevermarried persons were found to have lower rates of depression than those divorced, separated, and widowed. For example, in the ECA study, divorced and separated individuals had over a twofold increase compared to those married and never married (Table 70.2). Two countries with the lowest rate of MD in the ECA study—Korea and Taiwan—also had the lowest divorce and separation rate. Although Beirut also has a low rate of separation/divorce but a high rate of depression, the increased rate of depression may be more likely attributed to the civil war in the country that occurred around the same time as the study (1). Divorce and separation also increased the likelihood of the first depressive episode (7). The direction of the association is not clear.

Social Class

In the NCS, the odds ratios for MD were significantly higher for those individuals earning less than \$20,000 a year, and declined as income increased (6). With regard to employment status, homemakers had a very high risk of MD (odds ratios 2.8), but it is not clear whether the employment status has been adjusted for sex. Blazer et al. (6) reported no significant association in adjusted odds ratios for

TABLE 70.2. LIFETIME RATE PER 100 OF MAJOR DEPRESSION BY MARITAL STATUS: AGES 18 TO 64 YEARS^a

Country	Marital Status		Lifetime Rate/100 Major Depression		
	Separated/ Divorced (%)	Married (%)	Separated/ Divorced (%)	Married (%)	OR (95% CI) ^b
United States	12.2	57.3	11.0	4.3	2.5 (2.0–3.2)
Canada	11.4	59.1	23.8	7.6	4.1 (2.9-5.7)
Puerto Rico	9.6	59.0	7.7	3.8	1.9 (0.9-4.3)
France	6.1	75.5	39.6	14.2	3.8 (2.4-5.4)
Germany ^c	9.5	78.1	18.4	7.8	2.2 (0.8-6.1)
Lebanon ^d	0.3	50.6	100	19.4	NA
Taiwan (Taipei)	3.7	71.9	3.8	1.2	2.9 (1.6-5.5)
Korea (Seoul)	0.7	69.6	5.3	3.0	1.6 (0.3–7.3)
New Zealand	9.4	61.4	26.5	9.8	3.5 (2.1–5.9)

NA, not available.

^aData standardized to U.S. age and sex distribution (adapted from ref. 1).

^bOdds ratios (ORs) compare the rate of major depression in separated or divorced vs. married and are standardized to U.S. age and sex distribution and adjusted for age and sex within each site. Cl, confidence interval.

^cData from former Federal Republic of Germany (West Germany) based on ages 26 to 64 years.

^dBoth cases of major depression in separated or divorced study participants (2/2).

household income. In the ECA study, no association was found between socioeconomic status and MD. Although these findings are not conclusive, they suggest that socioeconomic status is not a strong risk factor for depression.

Race And Ethnicity

The prevalence of MD does not vary significantly with race and ethnicity, and in most cases can be explained by socio-economic and educational factors. Both major epidemiologic studies (ECA and NCS) controlled for socioeconomic status and education, and both showed that race was not a significant predictor of MD.

In the NCS the lifetime prevalence of MD was lower overall among African-American subjects, except for African-Americans 35 to 44 years of age. The highest prevalence, however, was in African-American women 35 to 44 years of age. No significant association was found in adjusted odds ratios for race/ethnicity in the study, which is consistent with the ECA study. The 10-country study (1) found the lowest rate of MD in the two Asian countries included—Korea and Taiwan. Neither the ECA nor the NCS studies had sufficient Asian samples to determine whether the risk increases for Asians living in the U.S.

Familial Factors

Methods used to assess possible heritability of MD are family, twin, and adoption studies. Although these studies are suggestive of a genetic vulnerability to MD, their design does not allow identifying the genetic variables involved in the mode of transmission. More direct genetic strategies include genetic linkage and association studies.

Family Studies

Family studies assess the rate of an illness in relatives of patients with the illness as compared with the rate in a

control group. The greater the difference in rates, the more likely it is that a genetic component exists. Gershon and colleagues (8) assessed rates of illness in relatives of unipolar probands and normal controls. They reported a lifetime risk of unipolar depression of 16.6% in the first-degree relatives of probands and 5.8% in those of normal controls (Table 70.3). Using these results and additional ones involving bipolar I, bipolar II, and schizoaffective disorder, the authors argued for a multifactorial genetic vulnerability model, ranging from unipolar to bipolar II, to bipolar I, and finally to schizoaffective disorder.

In a family study of 335 probands and 2,003 first-degree relatives, Weissman and colleagues (9) reported a lifetime rate of MD of 14.7 per 100 in the relatives of probands with mild depression, and a rate of 16.4 to 16.5 per 100 in the relatives of probands with severe depression, whereas the rate of MD in the relatives of control subjects was 5.1 per 100 (comparable to the rate in the general population). The distinction between mild and severe depression was made on the basis of hospitalization. Persons hospitalized for more than 5 days for a depressive episode met the criteria for severe depression, whereas persons with mild depression were those never hospitalized for depression.

The risk of depression is higher among the relatives of probands with early-onset recurrent MD. Bland et al. (10) reported a morbidity rate of 17.4% in relatives of probands with early-onset recurrent unipolar depression. This contrasted with 3.4% rate in relatives of probands with a single episode of depression and late age of onset. A study of 179 probands with recurrent depression found a morbid risk of 20.7% for nonbipolar depression (11). Consistent with Bland et al.'s study, relatives of probands with early-onset recurrent unipolar depression (before the age of 20) had a significantly higher risk of depression than relatives of lateonset probands (11). Similar results were obtained by Weissman et al. (12). The rates of MD were highest (24.2)

TABLE 70.3. FAMILY STUDIES OF MAJOR DEPRESSION

		Rate/100	
Form of Depression	Study	Proband	Control
Unipolar MDD	Gershon et al., 1982 (8)	16.6	5.8
Mild depression	Weissman et al., 1984 (9)	14.7	5.1
Severe depression		16.4-16.5	
Recurrent depression	Kupfer et al., 1989 (11)	20.7	NA
Single-episode, late onset	Bland et al., 1986 (10)	3.4	NA
Recurrent depression, late onset		8.2	
Single-episode, early onset		7.5	
Recurrent depression, early onset		17.4	
Early onset (age <20)	Weissman et al., 1984 (12)	24.2	4.8

MDD, major depressive disorder.

per 100) in the relatives of probands with early age of onset (younger than 20) and decreased to 7.6 per 100 in relatives of probands with late age of onset (over 40).

These findings have formed the rationale for an NIMH-sponsored multisite genetic sib-pair study of early-onset recurrent MD. Nearly 1,000 sib pairs will be diagnosed and DNA made available to the scientific community for genetic study.

A variant of family studies are studies of offspring of depressed parents. These studies consistently show a three-fold increased risk of MD in the offspring of depressed parents that is persistent as the offspring age and into the next generation (13–15). Interestingly, when parental divorce, parent-child bonding, and relationships were examined only, parental depression remained the only significant risk factor in the offspring of depressed parents. In the offspring of nondepressed parents, these factors were predictive of offspring depression. However, the rates of depression were low (16).

Twin Studies

In the early 1990s Kendler and his colleagues (17,18) reported a number of analyses of the data collected from female-female twin pairs identified through the populationbased Virginia Twin Registry. The proband-wise concordance was 37.3% in monozygotic (MZ) twins, and 23.9% in dizygotic (DZ) twins; the estimated heritability of liability to MD was 46% (17). However, when the model was corrected for unreliability of measurement, the heritability of liability to MD was estimated at 71% (18). In a more recent study that included female-female and male-male twin pairs identified through the same registry, Kendler and Prescott (19) found proband-wise concordance of 31.1% in MZ and 25.1% in DZ male twin pairs, and 47.6% compared to 42.6% in female twin pairs. These differences were statistically significant. The estimated heritability in male twins was 39%, comparable to the only other general population twin study of lifetime MD in men (20), who reported an estimated heritability of 36%. The estimated heritability in female twin pairs was 42% as measured in the previous report by the same authors (21). These rates are approximately twice those in the general population, reflecting a genetic component to MD.

In a hospital-based twin registry study conducted by McGuffin et al. (22), the proband-wise concordance was 46% in MZ and 20% in DZ twins, a statistically significant difference. The estimates of heritability were between 48% and 75%, based on the assumed population risk.

Personality

In contrast to most of the previously discussed risk factors that are fixed and clearly antedate the onset of depression (e.g., age and sex), personality is not fixed and in fact may interact with depression. Methodologic issues have confounded the study of this issue. For example, when depressed, patients may not provide valid reports of their premorbid functioning (23). In a comparison of patients' self-report personality measures first during their depressive episode and again following complete recovery 1 year later, the depressed state significantly influenced assessment of emotional strength, interpersonal dependency, and extraversion (24).

The most methodologically clear approach is to evaluate persons before they develop a depressive disorder. Hirschfeld et al. (25) conducted a premorbid personality assessment in a large sample at risk for the development of MD. The personality features most predictive of first onset of depression among middle-aged adults (age 31 to 41) were decreased emotional strength and increased interpersonal dependency. Among younger adults (age 17 to 30) no personality features were associated with subsequent MD. This may reflect that psychosocial factors become more important in late-onset depression, whereas genetic factors are more important in early-onset depression.

Life Events

Clinicians have long described a relationship between life events (particularly adverse interpersonal events) and the onset of depressive episodes. A series of studies conducted between the middle 1960s and 1990 using standardized instruments and diagnostic procedures did find corroboration of this relationship (26). Jenaway and Paykel (26) report that events involving loss (e.g., divorce, death) and threat of separation are associated with depression. There is little specificity to this relationship, as these events precede other illnesses as well.

Kendler et al. (27) investigated how genetic liability to MD and stressful life events interact in the etiology of MD in a study of 2,164 female twins. They found that the incidence of depression increased significantly in the month of occurrence of 13 stressful events. Four of the events termed "severe"—death of a close relative, assault, serious marital problems, and divorce/breakup—predicted the incidence of MD with the odds ratios of greater than 10. Genetic liability also had a significant impact on the onset of MD. The lowest probability of onset of MD was found in individuals with the lowest genetic liability (MZ, co-twin unaffected) for those exposed and unexposed to a severe event. Probabilities of the onset of MD were substantially higher in individuals with the highest genetic liability (MZ, cotwin affected). Kendler et al. concluded that genetic factors influenced the risk of MD in part by influencing the susceptibility of individuals to the depressive effect of life events.

Early Trauma

Trauma in early life has long been considered an etiologic factor in the pathogenesis of depression by clinical theorists.

This issue has been examined in a series of studies by Brown's group (28,29) at the University of London. In one study of 286 working-class mothers in England, 9% reported childhood sexual abuse (28). Of these 64% suffered a depression during the period of study. In a subsequent prospective study the same investigators (29) found that childhood neglect or abuse was strongly associated with early-onset (before age 20) depression. McCauley and colleagues (30) also found that childhood physical or sexual abuse was predictive of a variety of adult afflictions, including depression. Heim and colleagues (31) found that childhood abuse causes persistent hypothalamic-pituitary-adrenocortical (HPA) hyperactivity in adulthood, which is consistent with depression. In a review of this area, Kessler and colleagues (32) concluded that adverse childhood events were associated with early-onset depression. Caution is in order in interpreting these findings because multiple-year retrospective withdrawal can be flawed, and controlling for all relevant covariates (such as family history of depression) is often impossible.

General Medical Illness

Increased rates of depression have been reported among patients with several general medical illnesses. Among these are cardiovascular disease, AIDS, respiratory disorders, cancer, and several neurologic conditions (Parkinson's disease and stroke in particular) (33,34). The relationship is most striking in cardiovascular disease; 13 prospective studies using structured clinical diagnostic interviews evaluating antecedent depression on subsequent cardiovascular disease were reviewed by Musselman et al. (35). Almost all the studies found a strong association between depression and subsequent cardiovascular morbidity and mortality. Several important physiologic aspects of depression may account for this association. They include HPA dysregulation, sym-

pathomedullary hyperactivity, and diminished heart rate variability (35).

BIPOLAR DISORDER

Prevalence

The lifetime prevalence rate of bipolar I disorder reported in the NCS (2) was 1.6%, and the ECA study conducted in the United States reported a lifetime rate of 0.9% (36). In contrast to MD, the prevalence rates were remarkably consistent among countries (Canada, Finland, France, Germany, Hong Kong, Italy, Korea, New Zealand, Puerto Rico, Taiwan, and the United States), and there was little variation in rates by gender (Table 70.4). The rates of bipolar spectrum disorder (bipolar I, bipolar II, cyclothymia, and others) may be considerably higher than bipolar I alone (37). The prevalence rates reported in 11 studies of bipolar II disorder were between 0.3% and 3% (38). The lifetime prevalence rates for bipolar spectrum disorder were reported between 3% and 6.5% (38).

Gender and Age

In contrast to MD, epidemiologic data show no significant sex differences in rates of bipolar disorder (Table 70.4). No sex differences were reported in the ECA study (39). Similarly, the NCS reported no sex differences in either the mean number of total episodes of mania and depression combined (75.4 in men and 60.4 in women), and not a large sex difference in median number of total episodes (38 in men and 30 in women) (40). Additionally, no differences in male to female ratios of bipolar disorder were found internationally (1). Mean age of onset for bipolar depression was generally younger than for MD, ranging from 18 to 27 years of age in different countries (1). The NCS places the age of onset at 21.

TABLE 70.4. LIFETIME PREVALENCE OF BIPOLAR DISORDER^a

	Lifetime Rates/100				
	Overall	Females	Males	F/M Ratio	Mean Age at Onset
United States (ECA 1980)	0.9	1.0	0.8	1.2	18.1
United States (NCS 1990)	1.6	1.7	1.6	1.1	21.0
Canada, Edmonton	0.6	0.5	0.7	0.7	17.1
Puerto Rico	0.6	0.5	0.8	0.6	27.2
Germany ^b	0.5	1.0	0.0	NA	29.0
Taiwan	0.3	0.3	0.3	1.0	22.5
Korea	0.4	0.2	0.6	0.3	23.0
New Zealand	1.5	1.2	1.7	0.7	18.2

NA. not applicable.

^aRates have been standardized to the U.S. age and sex distribution (adapted from ref. 1).

^bIn Germany (former Federal Republic of Germany) the one study participant in Munich with bipolar disorder was female.

Other Sociodemographic Variables

Historically bipolar disorder was thought to be more frequent among higher socioeconomic classes, and there were some pilot data to support this (e.g., 41). However, population-based studies over the last two decades have not replicated this finding. In the ECA, occupation, income, and education were not found to influence prevalence (42). In the NCS, those with bipolar I disorder were more likely to have annual incomes less than \$20,000. The notion of higher rates of bipolar disorder among higher income levels was probably due to misdiagnosis of bipolar patients as schizophrenics in lower income groups.

In the ECA, bipolar disorder was much less frequent among married people, as contrasted with divorced or never-married people. Bipolar disorder was more prevalent among those with multiple divorces (42). In the NCS, bipolar disorder was more frequent among unmarried, poorly educated people.

Genetic and Familial Factors

In a review of the eight family studies of bipolar I disorder that included a control group, a metaanalysis (43) showed that bipolar I disorder was seven times more likely among relatives of bipolar I probands than of controls. These studies also demonstrate an increased risk of MD in relatives of bipolar probands, although the relative risk is lower than for bipolar I. Early age of onset and number of ill relatives increases the risk of illness in relatives, but other variables (e.g., type of relative) appear not to affect it (43).

In a pooled analysis of the six twin studies of bipolar I disorder conducted between 1962 and 1999, Craddock and Jones (43) calculated an estimate of proband-wise concordance of 50%, although the authors believe this to be an underestimate. They believe it is probably around 60%. Integrating the results of family, twin, and adoption studies, Craddock and Jones conclude that there is a substantial genetic predisposition to bipolar disorder.

There have been a number of investigations aimed at determining the actual genes involved in bipolar illness. Attempts to demonstrate linkage to the X-chromosome, to color blindness, to chromosomes 4, 11, 18, and others have not been conclusive (43). The most likely explanation for lack of success is that these strategies assume a single genetic mode of inheritance for a complex multiple-gene interaction with environmental factors.

Environmental Factors

Although biological and genetic factors have long been known to play a major role in the etiology of bipolar disorder, psychosocial factors are gaining attention. In particular, many studies have identified the association between stressful life events and social rhythm disruptions and onset of recurrence. It is unlikely that psychosocial factors play a major role in the risk of first onset of bipolar disorder, but they may have an important role in increasing the risk of recurrence.

Chrono-biological disturbances have long been associated with bipolar disorder (44). Sleep-wake and other circadian rhythm disturbances are core symptoms of bipolar episodes for both manic and depressive episodes (e.g., insomnia, and decreased need for sleep). Some have theorized that disruption in social zeitgebers (i.e., social demands or tasks that set the biological clock by environmental events) can lead to instability in circadian rhythms, which can in turn trigger bipolar episodes (45). Malkoff-Schwartz and colleagues (46) found than severe social rhythm disruptions (e.g., returning from international trips, moving, losing a job) were associated with onsets of mania, but not depression, in bipolar patients.

DISCUSSION

Beliefs and hypotheses about risk factors for depression (such as undue interpersonal dependency) emerged from clinicians treating individual patients and from studies done in psychiatric settings. Both suffer from sampling bias: those presenting for treatment are evaluated, but many factors in addition to the illness itself affect treatment seeking (e.g., income and psychological mindedness).

This chapter's introduction described the value of epidemiology in testing these hypotheses. The descriptive epidemiologic studies from around the world with their unbiased population samples have supported the validity of some of the hypotheses and have not supported others.

For MD there is strong evidence that women have two-fold the prevalence of men, an age of onset between 25 and 30 years, an increase following separation and divorce, and an increase in families of those with MD. There are significant differences in lifetime rates around the world. There is little support for racial, ethnic (with the possible exception of Asian), and income factors. Personality factors are non-specific. Early life trauma, particularly sexual abuse, is associated with early-onset depression in women. Increased rates of depression are found in several general medical illnesses. The association between depression and cardiovascular illness is strong, with depression predicting increased rates of morbidity and mortality among cardiovascular patients.

Analytic studies (such as twin studies) have suggested some interaction among genetic and environmental factors. The incidence of depression was increased when several life events (such as death of a close relative) occurred in the prior month in individuals with high genetic liability. The ongoing NIMH sib-pair study of early-onset depression will shed light on the possible genetic etiology of early-onset recurrent MD.

For bipolar disorder, there are substantial differences in

risk factors compared to MD. There is little variation in lifetime rates around the world (about 1%), and nearly equal prevalence in men and women. Bipolar spectrum is much more frequent, in the range of 3% to 6%. Age of onset is in the late teens and early twenties, earlier than in MD. A range of studies strongly support a genetic predisposition to bipolar disorder, but specific replicable genetic factors have yet to be demonstrated. A complex multiple gene interaction with environmental factors is most likely, a situation that is challenging to research and to isolate. Life events, especially disruptions in social zeitgebers, increase the likelihood of manic, but not depressive, recurrences in bipolar subjects.

An intriguing new area of interest is emerging in risk factors for depression—that of differences in consumption of fish oils around the world. Hibbeln (47) documented a strong negative correlation (-0.84) between the prevalence of MD and the annual apparent fish consumption per person in nine countries worldwide. He argued that this may be related to varying amounts of long-chain polyunsaturated fatty acids in diets in different cultures (48).

An experimental epidemiologic study is under way that will test genetic risk factors for bipolar disorder. Calabrese is prophylactically treating familially high-risk adolescents with a mood stabilizer in a longitudinal double-blind placebo-controlled study.

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