

# Premature Mortality From General Medical Illnesses Among Persons With Bipolar Disorder: A Review

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**Objective:** Despite recent evidence that patients with bipolar disorder are at increased risk of premature mortality resulting from general medical disorders, there has been no systematic review of published studies. The authors reviewed the literature to determine whether there is evidence of increased risk of mortality from general medical causes among patients with bipolar spectrum disorders. **Methods:** MEDLINE was searched from 1959 to 2007 with a focus on bipolar disorder and medical mortality. Published studies in English with more than 100 patients were included. **Results:** Seventeen studies were identified involving 331,000 patients with bipolar disorder, affective psychosis, affective disorder severe enough to require inpatient psychiatric care or treatment with lithium, or schizoaffective disorder (that is, bipolar spectrum disorders) meeting the inclusion criteria. Compared with age- and sex-matched control samples without mental illness in the general population, mortality ratios for death from natural causes and from specific general medical conditions, such as cardiovascular, respiratory, cerebrovascular, and endocrine disorders, were significantly higher among patients with bipolar spectrum disorders in most studies. This finding was more consistent in larger studies with more than 2,500 patients with bipolar spectrum disorders. Cumulatively, cardiovascular disorder appeared to be the most consistent cause of excess mortality in larger studies. **Conclusions:** The available evidence suggests that bipolar spectrum disorders are associated with increased premature mortality secondary to general medical illnesses. Unhealthy lifestyle, biological factors, adverse pharmacologic effects, and disparities in health care are possible underlying causes for this excess mortality. (*Psychiatric Services* 60:147–156, 2009)

Although several studies have found evidence that major depression is associated with increased risk of early mortality from general medical illnesses, fewer studies have investigated premature mortality from such illnesses among individuals with bipolar disorder (1). In the past, excess deaths associated with bipolar illness were attributed

mostly to unnatural causes, such as suicide, homicide, and accidents (2–5). Over the past decade, there is increasing evidence that patients with bipolar illness may be at higher risk of premature death from general medical disorders.

Emerging data indicate that although standardized mortality ratios are higher for unnatural causes (that

is, suicide and accidents), the majority of excess deaths among persons with bipolar disorder are secondary to comorbid general medical conditions. The causes of this excess mortality may include unhealthy diet (6), obesity (6,7), binge eating (8,9), sedentary lifestyle (6,10), smoking (11–13), social deprivation (14,15), living alone or being homeless or single (15,16), poor access to and less effective use of health services (17–21), biased attitudes among health care providers (18,22–30), failure of psychiatric providers to ask about or address medical problems (31–33), the “competing needs theory” (that is, health care providers might give precedence to conditions that need immediate attention while management of other conditions is delayed or forgotten) (34–36), and comorbid substance use disorders (37–40). Biologic factors associated with bipolar illness, such as stress-related effects on the immune system (41–45) and on the hypothalamic-pituitary axis (41,46,47), increased activity of the sympathetic nervous system (48,49), and metabolic side effects of pharmacologic treatments, may also increase the risk of mortality (50–55).

The association of psychopharmacologic agents with obesity and type 2 diabetes has also helped stimulate research about general medical outcomes of patients with severe mental illness. Olanzapine, which was approved in 2000, was the first second-generation antipsychotic to gain approval by the Food and Drug Administration for the treatment of acute mania and subsequently for maintenance treatment. Since then four oth-

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er second-generation antipsychotics have been introduced and approved for the treatment of bipolar disorder (56,57). Although second-generation antipsychotics have less risk than first-generation agents of side effects, such as extrapyramidal symptoms, tardive dyskinesia, and hyperprolactinemia, evidence shows that some of these medications are associated with obesity and metabolic abnormalities, which may increase morbidity and mortality resulting from diabetes and vascular disease (58,59). Many patients with bipolar disorder are treated with mood stabilizers that are also associated with increased risks of obesity and metabolic syndrome.

The aim of this study was to review the literature in regard to excess mortality attributable to medical problems among patients with bipolar spectrum disorders. Verification that bipolar disorder is associated with premature mortality from general medical illnesses could lead to development of health services models that integrate preventive medical interventions into community mental health settings. Given that most of the studies reviewed did not include structured psychiatric interviews, the following diagnoses were included in the definition of bipolar spectrum disorders used in this study: bipolar disorder, schizoaffective disorder, affective psychosis, and affective disorder severe enough to require inpatient admission or treatment with lithium.

## Methods

We searched the MEDLINE database from 1959–2007 using combinations of the following terms: bipolar, mania, or affective disorder and mortality, outcome, or follow-up. We also located additional studies by searching the citations from all the retrieved and other relevant articles. In addition, e-mails were sent to authors of selected articles if more information was needed. Several inclusion criteria were used for this review. Only English-language reports of studies with more than 100 patients were included. All studies included cause-specific standardized mortality ratios (SMRs) or mortality ratios (MRs) or SMRs or MRs due to natural causes

as a whole, or the studies provided sufficient information to calculate these measures. SMRs measure the excess or deficit in mortality in the selected study population compared with the age- and gender-specific death rates of a standard population. MRs measure the number of deaths per specific study population compared with a control group. All studies measured mortality rates among patients with bipolar disorder (either type I or II), schizoaffective disorder, affective disorder (severity level sufficient to require inpatient psychiatric admission or treatment with lithium), affective psychosis, or any combination of these. If there was more than one report describing results from the same study sample over time, the report with the longest follow-up period was included.

## Results

Through the electronic and manual searches, we identified 44 English-language articles. A total of 27 were excluded for the following reasons: eight articles reported studies that included fewer than 100 patients, seven articles presented data from studies that included patients with several psychiatric diagnoses (that is, we could not differentiate patients with bipolar spectrum illnesses), five articles reported on samples already included in another paper, five articles reported studies that did not separate suicide and nonsuicide mortality, and two articles reported studies that did not include a comparison group.

Our systematic review of the literature identified 17 studies that met the inclusion criteria. Tables 1 and 2 divide the studies into more generalizable samples, which we defined as those with more than 2,500 patients with bipolar spectrum illnesses (Table 1) and smaller studies with fewer than 2,500 patients with these illnesses and with samples selected on the basis of lithium use (Table 3).

In one of the larger studies, Laursen and colleagues (60) compared mortality rates among patients with severe mental illness who were admitted to a psychiatric hospital and rates among those without a history of psychiatric hospital admission in the entire adult population of

Denmark after controlling for age, gender, and calendar year. Among patients with bipolar or schizoaffective disorder, an inverse relationship was found between age group and mortality rate. Compared with persons without major psychiatric disorders, patients with either bipolar or schizoaffective disorder had significantly higher mortality risk in all age groups, but SMRs were highest in the younger age groups. In addition, SMRs were also higher for all natural causes of death (cardiovascular, respiratory, and endocrine conditions) except for cancer both among patients with bipolar disorder and among those with schizoaffective disorder.

Kisely and colleagues (61) studied mortality rates among patients who had received psychiatric treatment (inpatient and outpatient) in Nova Scotia, Canada, and compared these rates to those in the entire adult Canadian population. Controlling for age and gender, the regression analysis showed that an “affective psychosis” diagnosis was significantly associated with increased mortality risk (SMR=1.35, 95% confidence interval [CI]=1.24–1.47.) Among patients with affective psychosis, mortality risk from natural causes was not increased in most categories except for cerebrovascular disease and pneumonia or influenza.

Lawrence and colleagues (24) studied the rate of hospital admissions, revascularization procedures, and deaths from ischemic heart disease among more than 210,000 patients with mental illness and compared it with the rate in the general population of Western Australia, after adjusting for age and gender. Among patients with affective psychosis, mortality from ischemic heart disease was significantly higher for both sexes, although the hospital admission rate was not different from that in the general community. The rate of revascularization was significantly lower for psychiatric patients. Among users of mental health services, ischemic heart disease was responsible for 16% of excess deaths (foremost cause of excess deaths), compared with 8% of excess deaths caused by suicide.

**Table 1**

Characteristics and results of large studies (&gt;2,500 patients) of mortality among persons with bipolar spectrum illnesses

Author and year (reference)	Design	Patients	Control group	Results <sup>a</sup>
Laursen et al., 2007 (60)	Retrospective, using 3 registers of psychiatric inpatients (1973–2001); follow-up, 18 years; adjusted for age, gender, and year; <i>ICD-8</i> , -9, and -10 diagnoses	1st admission to a psychiatric unit; major depression, 72,165; schizophrenia, 17,660; bipolar disorder, 11,648; schizoaffective disorder, 4,055	Danish Civil Registration System; 5.6 million persons never admitted to a psychiatric unit	SMRs (95% CI) for natural causes by age group among males and females, respectively Bipolar disorder: ≤24 years, 5.4 (1.7–16.9) and 5.92 (1.5–23.7); 25–39 years, 3.6 (2.5–5.3) and 4.5 (3.2–6.5); 40–54 years, 3.2 (2.8–3.8) and 2.5 (2.2–3.0); 55–79 years, 1.7 (1.6–1.8) and 1.9 (1.8–2.0); ≥80 years, 1.4 (1.2–1.6) and 1.3 (1.2–1.4) Schizoaffective disorder: ≤24 years, 10.7 (2.7–42.9) (too few females to analyze); 25–39 years, 6.0 (3.9–9.4) and 3.8 (2.0–7.1); 40–54 years, 3.5 (2.8–4.5) and 3.0 (2.4–3.9); 55–79 years, 1.7 (1.4–1.9) and 1.8 (1.7–2.0); ≥80 years, 1.5 (1.1–2.0) and 1.3 (1.1–1.5) Cause-specific SMRs (95% CI) among males and females (all ages) Bipolar disorder: cardiovascular, 1.6 (1.4–1.7) and 1.7 (1.5–1.8); cancer, 1.0 (.9–1.2) and 1.0 (.9–1.1); respiratory, 2.9 (2.5–3.3) and 2.2 (1.9–2.5); endocrine, 2.5 (1.8–3.4) and 2.0 (1.5–3.7) Schizoaffective disorder: cardiovascular, 1.6 (1.3–2.0) and 1.6 (1.4–1.9); cancer, 1.1 (.9–1.5) and 1.0 (.9–1.3); respiratory, 2.5 (1.8–3.5) and 2.2 (1.7–2.8); endocrine, 4.2 (2.5–6.9) and 2.3 (1.5–3.7)
Kisely et al., 2005 (61)	Retrospective; 1st psychiatric contact in 1995–2000 of inpatients and outpatients; adjusted for age and gender; <i>ICD-9</i> and <i>DSM-IV</i> diagnoses	Total, 221,048	Adult Nova Scotia population from Canadian Vital Statistics database	SMRs (95% CI) for natural causes among patients with affective psychosis Myocardial infarction: ns Cancer: ns Diabetes: ns Cerebrovascular, 1.5 (1.0–2.1) Ischemic heart, ns Pneumonia and influenza, 2.6 (1.6–4.0) Chronic obstructive lung disease, ns
Lawrence et al., 2003 (24)	Retrospective review of records (1980–1998) from all private and public hospitals for patients with any contact with mental health outpatient services; matching of records to death register; adjusted for age and sex; <i>ICD-9</i> diagnoses	210,000 mental health service users; SMR calculated for 165,699 who had 1st contact with mental health system in 1980–1998; affective psychosis, 17,852	Adult death rate, Australian Bureau of Statistics (1980–1998)	SMR (95% CI) for ischemic heart disease for patients with affective psychosis: 1.6 (1.3–1.9) for males and 1.3 (1.1–1.6) for females
Osby et al., 2001 (62)	Retrospective inpatient chart review (1971–1995); adjusted for year of the 1st admission, age at 1st admission, and sex; <i>ICD-8</i> and -9 diagnoses	Bipolar disorder, 15,386 patients	Swedish register of cause of death, 1998	SMRs (95% CI) for patients with bipolar disorder among males and females, respectively All natural causes: 1.9 (1.8–2.0) and 2.1 (2.0–2.2) Cardiovascular: 1.9 (1.8–2.1) and 2.6 (2.4–2.9) Respiratory: 3.1 (2.6–3.7) and 3.2 (2.7–3.9) Cancer: ns and 1.2 (1.1–1.4) Cerebrovascular: 1.9 (1.5–2.4) and 2.0 (1.7–2.4)
Hoyer et al., 2000 (63)	Retrospective record review (1973–1993) for 1st-time inpatients with affective disorder; adjusted for age, gender, time since 1st admission, and year; <i>ICD-8</i> diagnoses	Total, 54,103; number of patients with bipolar and unipolar depression not reported separately	Danish statistics	SMRs (95% CI) for all patients with affective disorders among males and females, respectively Natural causes: 1.7 (1.6–1.7) and 1.5 (1.4–1.5) Cancer: 1.2 (1.1–1.2) and 1.1 (1.0–1.2) Cerebrovascular: 1.7 (1.5–1.9) and 1.4 (1.3–1.5) Cardiovascular: 1.6 (1.6–1.7) and 1.4 (1.4–1.5) Respiratory: 2.0 (1.8–2.2) and 1.9 (1.8–2.1) SMRs (95% CI) for natural causes for patients with bipolar disorder by follow-up period (both sexes) 0–1 year: 2.4 (2.0–2.8) 1–3 years: 1.6 (1.4–1.8) 3–5 years: 1.7 (1.5–2.0) >5 years: 1.5 (1.4–1.6)

<sup>a</sup> SMR, standardized mortality ratio

**Table 2**

Characteristics and results of smaller studies ( $\leq 2,500$  patients) of mortality among persons with bipolar spectrum illnesses

Author and year (reference)	Design	Patients	Control group	Results <sup>a</sup>
Dutta et al., 2007 (65)	Prospective (1965–1999); only patients with bipolar disorder I at 1st manic presentation; 25% presented as outpatients; mean length of follow-up, 19 years; adjusted for sex and age; <i>DSM-IV</i> diagnoses	Total, 235; mean age at first presentation, 30 for males and 35 for females	1991 population England and Wales	SMRs (95% CI) for all causes and for all natural causes for patients versus the general population: ns for both sexes Cause specific Cancer, ns for both sexes Cardiovascular and cerebrovascular, ns for both sexes Infections and respiratory: ns for males and 3.1 (95% CI=1.2–65.) for females
Angst et al., 2002 (5)	Prospective (1959–1963); inpatients with affective disorder, including schizoaffective, major depressive disorder, and bipolar I and II disorder; follow-up, 34–38 years; adjusted for age, gender, and observation period	Total, 406; bipolar (including schizoaffective) disorder, 220	Swiss national death registry	SMRs for patients with bipolar disorder All natural causes, 1.4 ( $p < .05$ ) Cancer, ns Cardiovascular, 1.8 ( $p < .05$ ) Cerebrovascular, ns
Saku et al., 1995 (68)	Retrospective (1948–1982); inpatients; adjusted for age group, year, and sex; <i>DSM-III-R</i> diagnoses	Schizophrenia, 2,268; bipolar, 187	Japanese statistics; adult mortality rates for 5-year periods	Only significant SMRs for bipolar group from natural cause: Hypertension: 5.6 ( $p < .05$ ) for females Pneumonia and bronchitis: 7.4 ( $p < .01$ ) for males
Sharma and Markar, 1994 (69)	Retrospective chart review (1970–1975); patients with $\geq 1$ episodes of mania; inpatients and outpatients not distinguished; follow-up, 12–17 years; adjusted for age and sex; <i>DSM-III</i> diagnoses	Bipolar, 472; average age, 66.4	Registrar General for Scotland; “similar group of adults in Scotland in 1978”	Significant MRs for patients with bipolar disorder Cardiovascular: 3.0 Respiratory: 3.1
Zilber et al., 1989 (66)	Retrospective; inpatients in Israel during 1978 for any psychiatric disorder; follow-up, 5 years; adjusted for age, sex, and ethnicity; <i>ICD-9</i> diagnoses	Affective disorder, 7,868 person-years	Israel Central Bureau of Statistics	SMRs for natural causes for patients with affective disorder All natural causes: 1.8 ( $p < .001$ ) Infectious: 14.8 ( $p < .001$ ) Cardiovascular and cerebrovascular: .3 ( $p < .001$ ) Cancer: ns
Black et al., 1987 (67)	Retrospective; inpatient population; follow-up, 2–14 years; adjusted for age, sex, and follow-up time, <i>ICD-9</i> diagnoses	Bipolar, 586	Iowa statistics; general population mortality rate	Significant SMRs for natural causes in follow-up of $\leq 2$ years Females with bipolar disorder, depressed phase, 7.0 ( $p < .001$ ) Males with bipolar disorder, manic phase, 3.3 ( $p < .05$ ) No significant SMRs for patients with bipolar disorder in follow-up $> 2$ years
Weeke and Vaeth, 1986 (70)	Retrospective record review; inpatients with 1st psychiatric admission in 1970–1972; adjusted for age and sex; <i>ICD-8</i> diagnoses of affective disorder	Affective disorder, 2,168; bipolar, 417; unipolar, 1,751	Danish Central Population Register	SMRs (95% CI) for natural causes for all patients with bipolar disorder or depression Cardiovascular: 1.6 (1.2–2.1) for males; ns for females Cancer: 1.5 (1.0–2.2) for males; ns for females
Haughland et al., 1983 (71)	Cross-sectional, 1 year; inpatients recruited 1975–1976; follow-up, 3.5 years; adjusted for age and sex; <i>DSM-II</i> diagnoses	Affective disorder, 144	New York State statistics, 1997	SMRs for patients with affective disorder Any cause: 4.7 for males and 2.4 for females, with most deaths due to cardiovascular disease
Tsuang et al., 1980 (72)	Prospective; inpatients at one site admitted from 1934–1944; follow-up, 30–40 years; adjusted for age, sex, and cause of death; <i>ICD-8</i> diagnosis	Bipolar disorder, 100; mean age, 34	Iowa annual mortality rate for 10-year periods	The only significant increase in observed to expected mortality was from circulatory disorders among females with bipolar disorder: 3.5 in 0–9 years after admission

<sup>a</sup> SMR, standardized mortality ratio; MR, mortality ratio

**Table 3**

Characteristics and results of smaller studies ( $\leq 2,500$  patients) of mortality among persons with bipolar spectrum illnesses who were being treated with lithium

Author and year (reference)	Design	Patients	Controls	Results <sup>a</sup>
Brodersen et al., 2000 (64)	Prospective; 133 inpatients started on lithium; follow-up, 16 years; adjusted for age, sex, and year; <i>ICD-8</i> diagnoses	Total (affective disorder), 133; depression, 23; bipolar, 61; unipolar or bipolar uncertain, 49; mean age, 43.0	Danish general population statistics	SMRs among patients with affective disorder Natural causes: 1.9 (95% CI=1.0–3.3) for males; 1.9 (1.1–3.0) for females; and 1.9 (1.3–2.7) for both sexes Cardiovascular disease, ns for both sexes
Nilsson, 1995 (73)	Prospective; inpatients with mood or schizoaffective disorders with $\geq 1$ admissions from 1970–1977, follow-up until 1991; adjusted for age and sex; <i>DSM-III-R</i> diagnosis	Total, 362; major depression, 78; bipolar, 240; schizoaffective, 44; 230 patients taking lithium, 132 not taking lithium; mean age, 48	Swedish Population Register and National Central Bureau of Statistics, 1980	SMRs for natural causes for patients taking and not taking lithium, respectively Pneumonia: 10.5 and 19.4 ( $p < .001$ ) Pulmonary embolism: 20.5 and 25.0 ( $p < .001$ )
Norton and Whally, 1984 (74)	Retrospective; patients taking lithium for $\geq 2$ months; follow-up, 10 years (1967–1976); adjusted for age and sex; research diagnostic criteria	Total, 791 affective disorders	Registrar General for Scotland, 1972	SMRs for patients with affective disorders Cardiovascular: 2.1 ( $p < .01$ ) Other natural causes: ns

<sup>a</sup> SMR, standardized mortality ratio; MR, mortality ratio

Osby and colleagues (62) studied mortality rates among more than 15,000 Swedish citizens who had a hospital discharge diagnosis of bipolar disorder and compared it with the mortality rate for the Swedish population. This study controlled for sex, age at admission, and calendar year. Among patients with bipolar disorder, SMRs from all natural causes were significantly higher for both sexes. Cardiovascular disease was the most frequent cause of death. This study showed that except for cancer and central nervous system diseases among males, all other natural causes of death were higher among patients with bipolar disorder.

In another Danish study, Hoyer and colleagues (63) investigated mortality and cause of death among more than 54,000 patients with affective disorder who were admitted to a psychiatric hospital. After the analyses controlled for age, gender, duration of illness since first psychiatric hospitalization, and calendar year, SMRs from all natural causes were higher among patients with affective disorder compared with the general population of Denmark. In the bipolar disorder subgroup, SMRs for natural causes were highest in the first year

after admission and decreased as duration of disease increased over the course of years.

The five studies discussed above were categorized as larger studies, that is, more than 2,500 patients. Twelve of the other studies reviewed were categorized as smaller studies with fewer than 2,500 patients (range 100 to 2,168) (64–74). The smaller studies may have been underpowered to find differences in mortality. Most of these studies compared specific medical causes of death among patients with affective disorders and a control group; only five studies reported SMRs for deaths from all natural causes (5,64–67). In a prospective study with an average follow-up period of 19 years, Dutta and colleagues (65) studied causes of death among 235 patients with newly diagnosed bipolar disorder. The study showed no increase in mortality from natural causes compared with the 1991 population of England and Wales, except for deaths from infectious and respiratory diseases among females. In another prospective study, over a 34- to 38-year period, Angst and colleagues (5) showed that SMRs for all natural causes and for cardiovascular disease (but not cere-

brovascular disease or cancer) were significantly higher among 220 inpatients with bipolar or schizoaffective disorder compared with the general population of Switzerland.

In a study in Japan, Saku and colleagues (68) found that SMRs among 187 patients with manic-depressive illness were significantly higher for hypertension among females and for pneumonia and bronchitis among males compared with adults in the Japanese population. In a retrospective British follow-up study over 17 years completed by Sharma and Markar (69), the MR from cardiovascular and respiratory disorders was significantly higher among 472 patients with bipolar disorder compared with a control group. In a five-year follow-up study, Zilber and colleagues (66) examined the risk of medical mortality for more than 7,868 person-years (the actual number of patients was not reported) among Israeli patients who had at least one inpatient psychiatric treatment for affective disorder during 1978. After the analyses controlled for age, sex, and ethnicity, the SMR for natural causes among patients with affective disorder was significantly higher than that in the general population of Israel.

The higher SMR for these patients was attributable to a higher mortality rate from infectious diseases, whereas the SMR attributable to cardiovascular and cerebrovascular disease together was significantly lower among patients with affective disorder.

Black and colleagues (67) compared mortality among 586 patients who had bipolar disorder with mortality in the general population of Iowa. In a follow-up period of less than two years, SMRs from natural causes were significantly higher among women with bipolar disorder who were depressed and men with bipolar disorder who were experiencing a manic episode. Using data from the Danish Central Psychiatric Register, Weeke and Vaeth (70) identified 417 patients with manic-depression and 1,751 with unipolar depression who had a first psychiatric admission between 1970 and 1972. Compared with the general population, SMRs for cardiovascular disease and cancer were both significantly higher among males, but not among females, with affective disorder. In a 3.5-year follow-up study by Haugland and colleagues (71), the SMR for all causes among 144 patients with affective disorder was significantly higher than the age-specific SMR in New York State. Most deaths were reported to be from heart disease. Tsuang and colleagues (72) studied causes of death among 525 patients with severe mental illness over 30 to 40 years. In the subgroup of 100 patients with mania, the observed to expected mortality ratio for circulatory system diseases among women, but not among men, was significantly higher than in the general population of Iowa over a nine-year follow-up period.

We also reviewed studies with small samples in which patients were selected because they were being treated with lithium. In a Danish prospective study by Brodersen and colleagues (64), 133 patients with affective disorder were started on lithium and followed up for 16 years. Regardless of medication adherence, trends for higher SMRs for all natural causes were found for both sexes, although the all-cause SMR was statistically significant only for female patients.

The SMR for cardiovascular disease was not different from that in the general population. Nilsson (73) investigated mortality among 362 patients with a mood disorder or schizoaffective disorder who were treated with lithium for at least one year. Compared with the adult Swedish population, cause-specific SMRs were higher for pneumonia and pulmonary embolism among the patients both when they were taking lithium and when they were not taking lithium. In a Scottish retrospective study by Norton and Whalley (74), 791 patients with affective disorder who had received lithium for at least two months during the ten-year follow-up had a significantly higher SMR for cardiovascular disease compared with the general population of Scotland.

## Discussion

### *Findings and implications*

This literature review showed that individuals with bipolar spectrum disorders appear to be at significantly higher risk of premature death from natural causes compared with the general population. The review of larger studies with at least several thousand participants indicated that persons with bipolar or schizoaffective disorder or severe affective disorder had consistently higher mortality rates from natural causes. Higher mortality from natural causes among patients with bipolar spectrum disorders ranged from 35% higher than a comparison group to twofold higher. The increased mortality rate is similar to the increased risk of mortality associated with smoking. Data from the National Health and Nutrition Examination Survey found that being a current smoker was associated with a 20% to approximately twofold increase in mortality among middle-aged and older men and women in the community, depending on age group (higher risks were found in younger age groups) (75).

In the larger studies the higher mortality was attributable to almost every cause of death that was investigated, such as cardiovascular, respiratory, cerebrovascular, and endocrine disorders. Deaths from neoplasms either were not higher or were slightly

elevated despite the probable higher number of risk factors for cancer (such as smoking and obesity) in this population. Among all causes of death, cardiovascular disease seemed to be responsible for the majority of excess deaths; the mortality risk was 35% to 2.5-fold higher. Studies that examined mortality from natural causes in different age groups or groups with different durations of illness found that as age or duration of illness increased, mortality from natural causes decreased (60,63).

Review of the smaller studies with fewer than 2,500 patients generally showed findings similar to but less consistent than those of the larger studies. Most studies showed higher mortality attributable either to natural causes or to several specific medical illnesses. In several small studies, mortality from cardiovascular disease was higher among persons with bipolar spectrum disorders. However, one of these smaller studies actually showed that the combined mortality rate from cardiovascular and cerebrovascular diseases was significantly lower among patients with affective disorder (66). The inconsistent results of the small studies may be due to chance or to use of samples that were less representative of patient or control populations.

Excess mortality from natural causes among patients with bipolar spectrum disorders may result from several mechanisms. Patients with bipolar spectrum disorders are more likely to smoke and to smoke heavily and might have higher exposure to second-hand smoke (11–13). In addition, bipolar disorder is highly comorbid with alcohol and other substance abuse (6,37). These patients are more likely to have a poor diet and sedentary lifestyle with resultant weight gain and obesity, which is more prominent during the depressive phase of the disorder and can further jeopardize health and increase mortality (6–10).

Several biologic mechanisms may contribute to the increased mortality risk from natural causes found among patients with bipolar disorder. Chronic stress is associated with increased cortisol levels, lack of cortisol suppression, and changes in the hypothalamic-pituitary-adrenal axis

responses. Both phases of bipolar disorder act as chronic stressors and lead to dysregulation of the hypothalamic-pituitary-adrenal axis and increases in cortisol levels (76,77). Chronic dysregulation of the hypothalamic-pituitary-adrenal axis and high levels of cortisol may increase insulin resistance, which can lead to hyperglycemia, increased oxidative stress, metabolic syndrome, and atherosclerosis (46,47). In addition, increased activity of the hypothalamic-pituitary-adrenal axis may be associated with hyperactivity of the sympathetic nervous system, a finding that is commonly observed among patients with bipolar disorder (48,49). Dysregulation of the autonomic nervous system may also lead to insulin resistance and may worsen metabolic syndrome (78) and also lead to an increased risk of sudden cardiac death. Interleukin-6 is one of several inflammatory markers that are higher among patients with bipolar disorder (43). Interleukin-6, by stimulating corticotrophin-releasing factor, can lead to hypothalamic-pituitary-adrenal axis hyperactivity and hypercortisolemia (79), which can lead to increased morbidity and mortality (41–45). Medications used to treat bipolar disorder may also increase the risk of diabetes and cardiovascular disorder.

Most patients with bipolar disorder are treated with mono- or polypharmacy, including at least one mood stabilizer with or without a second-generation antipsychotic (80). Most mood stabilizers are associated with weight gain (50–52). Most second-generation antipsychotics (with the exception of ziprasidone and aripiprazole) are also associated with increased risk of weight gain, diabetes mellitus, and impaired glucose and lipid metabolism, all of which can increase mortality from cardiovascular disease (53–55). Increased weight gain and change in body fat distribution can lead to insulin resistance, type 2 diabetes mellitus, and dyslipidemia, all of which may result in increased mortality from cardiovascular disease. Second-generation antipsychotics can also increase triglycerides via 5-HT<sub>2</sub> receptor blockade and further impair lipid metabolism (81).

Emerging data have shown that patients with severe mental disorders often receive lower-quality medical care, including post-myocardial infarction cardiovascular procedures and care (24,25,29,30), diabetes care (21,82–85), preventive medical care (86,87), treatment of hypertension (85,88), and treatment for dyslipidemia (85). Disparities in the quality of medical care of patients with mental illnesses can be ascribed to diverse factors. At one level, a person with mental illness may not be able to effectively communicate with providers and express concerns because of cognitive disturbance or affective instability (89,90). At the provider level, the non-psychiatrist physician's bias against persons with mental illness can adversely affect medical management of the patient and lead to poor-quality care (22,23). Psychiatrists and other mental health providers may also prioritize psychiatric issues and neglect medical problems (35,36). They may also feel uncomfortable treating certain medical problems or lack experience in treating certain problems (91). At the national level, lack of private insurance, poor access to health services, and the fragmented mental and physical health care systems are additional factors that may lead to disparities in medical care for individuals with mental illness (20,24,29,83,92).

New models of care may be necessary to improve general medical and psychological outcomes of patients with mental illness. Collaborative care models that integrate depression care coordinators and mental health specialists into primary care have been shown in 37 studies to be practical, cost-effective models to improve quality of depression care, patient satisfaction, treatment adherence, and depression outcomes (93). Recent studies that have tested integrating primary care clinicians into community mental health settings to provide preventive medical interventions have shown improved physical health of patients with chronic general medical illness and substance use disorders who were treated with these new models of care (94). More research needs to be planned to test ways to improve gen-

eral medical outcomes of patients with chronic mental illnesses such as bipolar disease.

### *Limitations*

In this literature review, limitations were noted in three categories: the systematic review process, methodologic problems in large studies, and methodologic problems in small studies. The systematic review was limited in that we had to combine literature on bipolar spectrum disorders (affective psychosis, affective disorder, schizoaffective disorder, manic-depressive disorder, and bipolar disorder) because of the paucity of studies in which the sample included only persons with bipolar disorder. We did not include articles that were in languages other than English. In most of the studies included in the review, structured psychiatric interviews were not used to establish diagnoses. Use of the different inclusion and exclusion criteria made it difficult to compare studies or standardize findings from the studies we reviewed. We were unable to measure whether exposure to second-generation antipsychotic agents was associated with increased mortality rates. Inclusion of patients with schizoaffective disorder and affective disorder may have led to overestimation or underestimation, respectively, of the association of bipolar illness with mortality.

In the second category, limitations of the larger studies included the fact that all used retrospective designs, limiting evaluation of causality. Larger studies (as well as small retrospective studies) collected administrative data or reviewed medical records, and thus information about many potential confounders, such as smoking or obesity, was not available. Use of medical records or administrative data is also subject to recording bias because the more severe medical disorders are likely to have been diagnosed. In addition, the diagnoses were made by individual psychiatrists in different parts of the world at different times and with different diagnostic and coding systems. The lack of standardized research criteria and the ongoing modification of the diagnostic criteria for bipolar disorder over time can challenge the reliability and validity of the

diagnosis in studies that are based on record linkage and registers. Future large prospective studies should be planned with representative community populations of respondents with and without a diagnosis of bipolar illness (a diagnosis that is based on a structured psychiatric interview) and with controls for socioeconomic factors and medical and psychiatric comorbidity; such studies should also examine behavioral risk factors (smoking, lack of exercise, obesity, and use of psychiatric medications) and quality of medical and psychiatric care as potential mediators of premature medical mortality.

In the third category, unique limitations of the smaller studies (fewer than 2,500 patients) included the fact that except for three small longitudinal studies (5,67,76), all other studies used retrospective designs that limited evaluation of causality. Also, because of small samples, these studies were probably underpowered to detect the differences in MRs that have been shown in larger studies, and only five of the 12 smaller studies measured mortality rates from all natural causes.

## Conclusions

This review strongly suggests that patients with bipolar spectrum disorders are at increased risk of premature death from general medical conditions. Given the increasing concern about premature mortality from diabetes and heart disease among patients with chronic mental illness, a 2004 consensus panel that included psychiatrists, endocrinologists, and internists made detailed recommendations for psychiatrists to monitor the risk of metabolic syndrome among patients taking second-generation antipsychotics and, more recently, mood stabilizers (95). These recommendations may help decrease the risk of obesity, diabetes, and vascular disease resulting from psychiatric medications among patients with chronic mental illness. However, patients with severe mental illness often have adverse health habits (such as poor diet, smoking, and lack of exercise), adhere poorly to medical regimens, and experience disparities in quality of medical care.

New models of care that integrate primary care physicians into clinics that treat patients with chronic medical illness need to be developed and tested.

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