Suicide and Attempted Suicide in Bipolar Disorder: A Systematic Review of Risk Factors

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Objective: To determine the main risk factors for suicide and nonfatal suicidal behavior in patients with bipolar disorder through a systematic review of the international literature.

Data Sources: Studies were identified through electronic searches of MEDLINE (1966–December 2003), EMBASE (1980–December 2003), PsycINFO (1872–November 2003), and Biological Abstracts (1985–December 2003) using index and free-text search terms for bipolar disorder, bipolar depression, manic depression, mania, and affective disorders; combined with terms for self-harm, self-injury, suicide, attempted suicide, automutilation, self-mutilation, self-poisoning, and self-cutting; and combined with terms for risk, case control, cohort, comparative, longitudinal, and follow-up studies. No language restrictions were applied to the search.

Study Selection: Included studies were cohort, case-control, and cross-sectional investigations of patients with bipolar disorder in which suicide (13 studies) or attempted suicide (23 studies) was reported as an outcome. The selected studies also used diagnostic tools including the DSM, *International Classification of Diseases*, and Research Diagnostic Criteria.

Data Synthesis: Meta-analysis of factors reported in more than 1 study identified the main risk factors for suicide as a previous suicide attempt and hopelessness. The main risk factors for nonfatal suicidal behavior included family history of suicide, early onset of bipolar disorder, extent of depressive symptoms, increasing severity of affective episodes, the presence of mixed affective states, rapid cycling, comorbid Axis I disorders, and abuse of alcohol or drugs.

Conclusions: Prevention of suicidal behavior in patients with bipolar disorder should include attention to these risk factors in assessment and treatment, including when deciding whether to initiate treatment aimed specifically at reducing suicide risk.

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Bipolar disorder (manic-depressive disorder) is associated with a significant risk of suicide, with approximately 10% to 15% of bipolar disorder patients dying by suicide.[1,2] Attempted suicide (deliberate self-harm) is also common in bipolar disorder, with between 20% and 56% of patients having a history of nonfatal self-poisoning or self-injury.[1] Risk factors for both suicide and attempted suicide in bipolar disorder patients are likely to include at least some of those for suicidal behavior in the general population. However, there may be additional risk factors related to the nature of the illness. Identification of these factors is important in order to assist clinicians in the detection of those at risk, especially now that evidence is growing for the likely specific antisuicidal effect of lithium.[3]

Previous reviews of risk factors for suicide and attempted suicide in bipolar disorder[4,5] have highlighted the importance of depression and alcohol abuse in suicide risk and also suggested increased risk in subtypes of bipolar disorder, including bipolar II disorder (depression with hypomania but not mania). However, these reviews have been largely descriptive and have not assessed the included studies for type of design. Systematic review procedures and meta-analysis of results of studies offer the most objective means of aggregating and summarizing findings from individual investigations.

We have conducted a systematic review of cohort, case-control, and cross-sectional studies of patients with bipolar disorder in which the outcomes of suicide and attempted suicide or deliberate self-harm have been presented.

METHOD

Studies were selected for inclusion in this review if they met the following criteria:

1. An *International Classification of Diseases* (ICD)-10 diagnosis of bipolar affective disorder (F31), or a DSM-IV diagnosis of bipolar I disorder (296.0, 296.4, 296.5, 296.6, 296.7) or bipolar II disorder (296.89). Samples using the following earlier versions of bipolar disorder diagnostic criteria were also included: ICD-8 (296.10, 296.30, 298.10), ICD-9 (296.0, 296.2–296.9), Research Diagnostic Criteria (including the earlier Feighner criteria[6] and the Schedule for Affective Disorders and Schizophrenia, lifetime version[7]), DSM-III, and DSM-III-R.
2. At least 90% of the subjects were aged 16 years or over.
3. The design of the study was a cohort study with a minimum follow-up period of 1 year, a case-control study, or a cross-sectional study.
4. An outcome of suicide or attempted suicide (including deliberate self-harm) was reported.
5. Specific risk factors for suicide or attempted suicide were investigated.

Search Strategy

A broad search strategy for potential articles was used in order to include all relevant studies. Electronic searches of MEDLINE (1966–December 2003), EMBASE (1980–December 2003), PsycINFO (1872–November 2003), and Biological Abstracts (1985–December 2003) were conducted using index and free-text search terms for bipolar disorder, bipolar depression, manic depression, mania, and affective disorders; combined with terms for self-harm, self-injury, suicide, attempted suicide, automutilation, self-mutilation, self-poisoning, and self-cutting; and combined with terms for risk, case control, cohort, comparative, longitudinal, and follow-up studies. No language restrictions were applied to the search. Non–English language articles were translated by people fluent in the relevant language with guidance from one of the researchers.

The identified studies were independently screened for suitability by 2 investigators. When differences of opinion occurred, these were resolved by discussion. When disagreements could not be resolved in this way, they were discussed with a third member of the research team, and consensus was thereby reached. When a study was reported in more than 1 article, data were extracted from the most recent report, and from both if different variables were reported in each article. Bibliographies of eligible articles were checked for possible relevant studies. International experts in the field were consulted to check whether there were any omissions from our identified studies and whether they knew of any additional unpublished studies. When there was any uncertainty about the data, authors were approached for clarification. Some authors also supplied original data. Only 1 non–English-language article was eligible.

Design of Studies

Each identified study was categorized using the following order to reflect strength of study design[8]: (1) prospective cohort study; (2) retrospective cohort study; (3) case-control study and, in addition, for attempted suicide; (4) cross-sectional case-control study; and (5) cross-sectional case-control study of lifetime history of attempted suicide. Unless it was specifically stated that attempted suicide occurred following onset of bipolar disorder, it was assumed that it may also have occurred before the onset of the disorder, and such studies were therefore put into category 5.

Data Extraction

Data were extracted from the reports independently by 2 members of the research team using a structured proforma that consisted of a list of variables and cells for recording total numbers of cases and controls, and the numbers of each group positive for a specific variable.

Suicides or suicide attempters were considered as cases, and those subjects without suicidal behavior as controls. Data on the presence or absence of individual potential risk factors in cases and controls were analyzed. The main results presented are those of meta-analyses of variables for which data were available from more than 1 study. Results of some of the findings for variables examined in single studies only are presented where they have relevance to the meta-analytic results or where they have been implicated in suicide risk in reviews or other research.

Statistical Analysis

Study results were combined using the DerSimonian and Laird random effects method of meta-analysis.[9] Risk factors were expressed as odds ratios or weighted mean differences, with 95% confidence intervals. Between-study heterogeneity was tested using Cochran's Q.

RESULTS

Search Results

The number of articles identified through the search strategy was 2142, of which 1906 did not fulfill the broad eligibility criteria. The remaining 236 articles were retrieved for detailed examination, and 181 did not meet the detailed eligibility criteria. Of the remaining 55 articles, 18 included data on suicide, and 40 on attempted suicide. Three articles included data on both outcomes. The included articles reported on 13 studies of suicide (Table 1) and 23 studies of attempted suicide (Table 2).

Table 1. Studies of Suicide Included in the Review

Authors, Date, Place	Study Design[a]	Study Description[b]	Diagnostic Criteria[c]	Suicides, N	Controls, N
Angst et al, 2002, Switzerland[12]; Angst and Preisig, 1995, Switzerland[11,d]; Angst, 1986, Switzerland[10,d]	1	Patients with affective disorder hospitalized between 1959 and 1963. Results for bipolar patients reported separately. Follow-up period: 34–38 y	DSM-III	18	199
		As above. Follow-up period: 27 y		18	202
Black et al, 1988, United States[19]; Black et al, 1987, United States[18,d]	2	Patients with affective disorder admitted between Jan 1970 and Dec 1981. Results for bipolar patients reported separately. Follow-up period: ≤ 14 y	DSM-III	7	579
Brown et al, 2000, United States[13]	1	Psychiatric outpatients consecutively evaluated between Jan 1975 and Dec 1995. Results for bipolar patients supplied by author. Median follow-up period for entire study: 10 y (range, <1 y–20 y)	DSM-IV	7	263
Coryell et al, 2003, United States[16];	1	Patients with bipolar disorder or schizoaffective disorder (manic type) admitted as inpatients or outpatients between 1978 and 1981, recruited to the NIMH Collaborative Program on the Psychobiology of Depression. Multicenter study. Mean (SD) follow-up period: 13.7 (6.1) y. Exclusions: nonwhite, IQ < 70, age < 17 y, primary language not English, organic mental disease, terminal illness, no knowledge of both biological parents	RDC	14	331
Coryell et al, 2001, United States[15,d]; Coryell et al, 1992, United States[14,d]		Patients with manic disorder or schizoaffective disorder (manic type) from above study. Mean (SD) follow-up period: patients who began with psychotic features: 11.1 (5.3) y; patients who began with nonpsychotic mania: 11.2 (4.9) y		3	136
Dunner et al, 1976, United States[20]	2	Patients with primary affective disorder admitted between July 1960 and Sept 1969. Results for bipolar patients reported separately. Follow-up period: 1–9 y	Feighner criteria	8	82
Høyer, 2002, Denmark[24]	3	Patients identified from the Danish Psychiatric Central Register who were admitted to any Danish hospital during 1994 and 1995 and committed suicide during inpatient treatment or less than 1 y after hospital discharge. Controls: living patients matched for diagnosis, sex, age, duration of time since first admission, date of index admission, and inpatient/outpatient status, including the date of discharge from the index admission. Results for bipolar patients supplied by author	ICD-10	27	27
King et al, 2001, United Kingdom[25]	3	Patients who committed suicide between 1988 and 1997 within 1 y of hospital discharge. Controls: living patients matched for diagnosis, age, sex, and date of admission. Results for bipolar patients supplied by author	ICD-9/ICD-10	12	18
Lenzi et al, 1999, Italy[17]	1	Female patients consecutively admitted for an affective or schizoaffective episode during 1989. Results for bipolar patients reported separately. Follow-up period: 3 y	DSM-III-R	3	95
Nordström et al, 1995, Sweden[21]	2	Mood disorder patients admitted during 1973–1987. Results for bipolar patients reported separately. Mean follow-up period for entire study group: 6 y (range, 1–11 y)	DSM-III	4	51
Ösby et al, 2001, Sweden[22]	2	Swedish Case Register study of bipolar and unipolar patients first admitted to any Swedish hospital between 1973 and 1995. Exclusions: patients aged > 70 y. Results for bipolar patients reported separately. Mean follow-up period: 10 y	ICD-8/ICD-9	672	14,714
Steblaj et al, 1999, Slovenia[26]	3	All inpatient suicides between 1984 and 1993. Controls: selected from inpatients in 1993–1995; matched for diagnosis, age, sex, and time of admission. Results for bipolar patients supplied by author	ICD-9	7	7
Tsai et al, 2002, Taiwan[27]	3	Bipolar I patients from a group of mood disorder patients admitted to hospital between Jan 1985 and Dec 1996 who later committed suicide. Controls: living patients from the same group matched for diagnosis, age, sex, and date of index admission	DSM-IV	41	41
Tsuang, 1978, United States[23]	2	Patients with schizophrenia or affective disorders consecutively admitted to hospital between 1935 and 1944. Results for bipolar patients reported separately. Follow-up period: 40 y	Feighner criteria	6	86

[a]1 = prospective cohort, 2 = retrospective cohort, 3 = case-control.
[b]Subjects and controls, source, date of recruitment, follow-up period, important exclusion criteria, other details.
[c]Bipolar disorder only unless otherwise stated.
[d]Report from the same study usually including a smaller and/or overlapping subject sample or shorter follow-up period.
Abbreviations: ICD = *International Classification of Diseases*, NIMH = National Institute of Mental Health, RDC = Research Diagnostic Criteria.

Table 2. Studies of Attempted Suicide Included in the Review

Authors, Date, Place	Study Design[a]	Study Description[b]	Diagnostic Criteria[c]	Attempted Suicides, N	Controls, N
Cassano et al, 1992, Italy[52]; Perugi et al, 1988, Italy[51,d]	5	Consecutive series of patients presenting with major depression as the index episode. Exclusions: comorbid Axis I disorder Results for bipolar patients reported separately	DSM-III-R	26	103
Coryell et al, 2003, United States[16];	1	Bipolar (I or II) or schizoaffective disorder (manic type) patients admitted as inpatients or outpatients between 1978 and 1981, recruited to the NIMH Collaborative Program on the Psychobiology of Depression. Multicenter study. Mean (SD) follow-up period: 13.7 (6.1) y. Exclusions: nonwhite, IQ < 70, age < 17 y, primary language not English, organic mental disease, terminal illness, no knowledge of both biological parents	RDC	116	229
Coryell et al, 2001, United States[15,d]; Coryell et al, 1992, United States[14,d];		Patients with manic disorder or schizoaffective disorder (manic type) from above study. Mean (SD) follow-up period, patients who began with psychotic features: 11.1 (5.3) y; patients who began with nonpsychotic mania: 11.2 (4.9) y		29	110
Coryell et al, 1989, United States[29,d]; Coryell et al, 1987, United States[28,d];		Major affective disorder patients recruited to above NIMH study. Follow-up period: 5 y. Results for bipolar patients reported separately		20	97
Endicott et al, 1985, United States[63,d]	5	Major affective disorder patients recruited to above NIMH study evaluated at intake episode. Results for bipolar patients reported separately		45	133
Dalton et al, 2003, Canada[35]	5	Patients with bipolar I, bipolar II, or schizoaffective disorder (bipolar type) recruited from newspaper advertisements and hospital clinics. Subjects from 305 families originally recruited for genetic study. Sample includes parents and siblings of 31 subjects	DSM-IV	86	250
Dunner et al, 1976, United States[20]	5	Patients with affective disorder randomly selected from those admitted between July 1960 and April 1971. Results for bipolar patients reported separately	Feighner	20	25
Feinman and Dunner, 1996, United States[36]	5	Bipolar outpatients seen by 1 author between Jan 1992 and Dec 1993. Exclusions: bipolar illness secondary to head trauma, monoamine oxidase inhibitor use, or other psychiatric illness other than substance abuse	DSM-IV	73	115
Goldring and Fieve, 1984, United States[37]	5	Affective disorder inpatients and outpatients. Exclusions: current substance or alcohol abuse, neurologic illness, or active medical conditions. Results for bipolar patients reported separately	SADS	35	47
Grunebaum et al, 2001, United States[50]; Oquendo et al, 2000, United States[49,d]	5	General psychiatric inpatients and outpatients. Exclusions: current substance or alcohol abuse, neurologic illness, active medical condition. Results for bipolar patients reported separately	DSM-III-R	25	31
		Bipolar disorder (I or NOS) inpatients. Age: 18–75 y. Exclusions: current substance or alcohol abuse, neurologic illness, current confounding conditions	DSM-III-R	21	23
Hantouche et al, 2003, France[38]	5	Bipolar patients hospitalized for an episode of acute mania. French national collaborative multisite EPIMAN-II-Mille study. Exclusions: schizophrenia, organic brain disorder. Age 18–65 y	DSM-IV	316	570
Leverich et al, 2003, United States, Germany, and Netherlands[48]; Leverich et al, 2002a, United States, Germany, and Netherlands[46,d]; Leverich et al, 2002b, United States and Netherlands[47,d]; Dittmann et al, 2002, Germany[45,d]; Suppes et al, 2001, United States and Netherlands[44,d]; McElroy et al, 2001, United States and Netherlands[43,d]	5	Patients with bipolar disorder (I, II, or NOS) or schizoaffective disorder (bipolar type). Stanley Foundation Bipolar Network, multisite clinical trials network	DSM-IV	219	429
				75	186

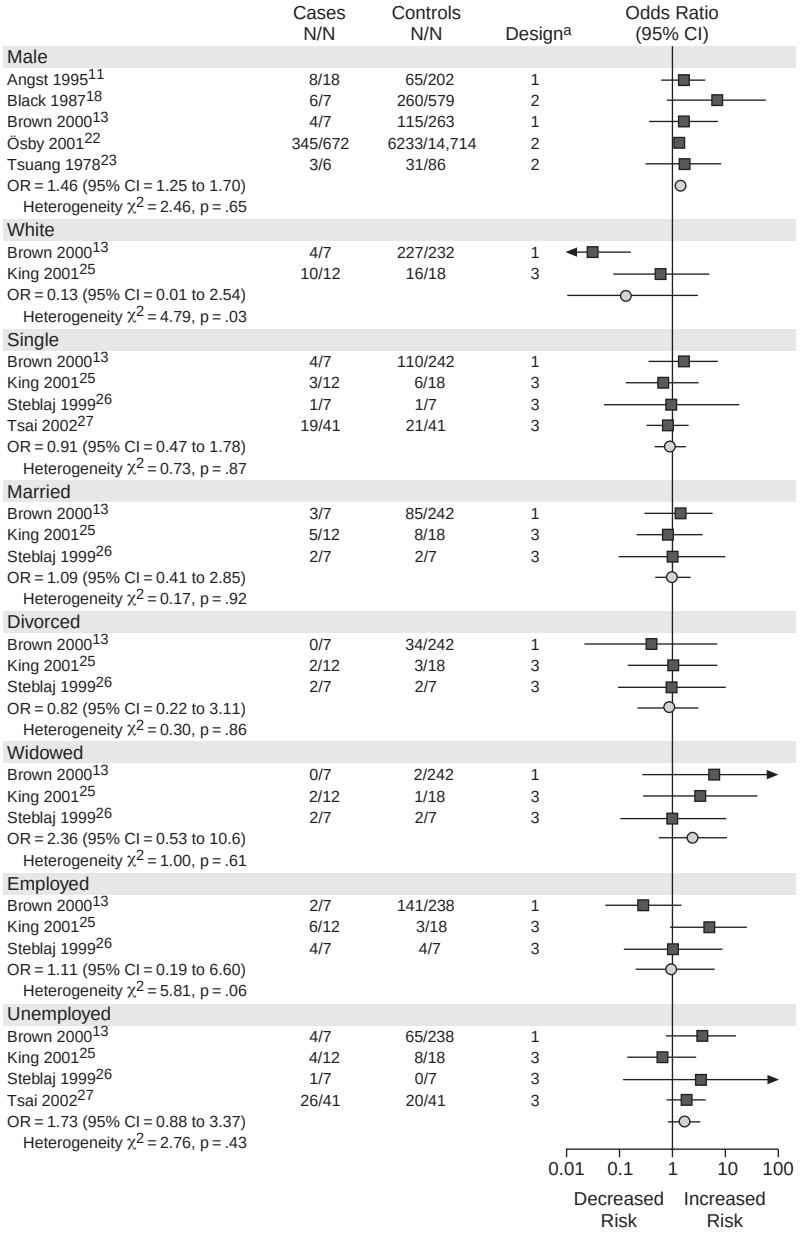
(continued)

Table 2. Studies of Attempted Suicide Included in the Review (cont.)

Authors, Date, Place	Study Design[a]	Study Description[b]	Diagnostic Criteria[c]	Attempted Suicides, N	Controls, N
Linkowski et al, 1985, Belgium[39]	5	Patients with major depression admitted between Dec 1978 and May 1984. Results for bipolar patients reported separately	RDC	65	179
López et al, 2001, Spain[40]	5	All bipolar I disorder inpatients and outpatients assessed between Feb 1994 and Dec 1996	DSM-III-R	56	113
MacKinnon et al, 2003, United States[41]	5	Patients with bipolar disorder or schizoaffective disorder (bipolar type) from families with 1 proband with bipolar I disorder and at least 1 other first-degree relative with bipolar I disorder or schizoaffective disorder (bipolar type) recruited for the NIMH Bipolar Disorder Genetics Initiative. Multicenter study	RDC	202	401
Maj et al, 1994, Italy[42]	5	Bipolar disorder patients with rapid cycling referred between Jan 1979 and Dec 1990. For each patient with rapid cycling disorder enrolled during each y, 2 nonrapid cyclers were randomly recruited. History of deliberate self-harm recorded at time of entry to study	RDC	34	77
Perugi et al, 1997, Italy[53]; Perugi et al, 2000, Italy[54,d]	5	Mixed-state and manic patients consecutively admitted to inpatient and day-hospital care from Jan 1990 to Sept 1992	DSM-III-R	69	192
Potash et al, 2000, United States[55]	5	Bipolar I probands and their first- and second-degree relatives with affective disorder from 71 families in a genetic linkage study. Results for bipolar patients reported separately	RDC	71	180
Serretti et al, 2002a, Italy[56]; Serretti et al, 2002b, Italy[57]	5	Consecutively admitted inpatients and outpatients with major depressive disorder or bipolar disorder admitted. Results for bipolar patients reported separately	DSM-III-R/ DSM-IV	177	448
		Bipolar inpatients and outpatients first admitted between 1993 and 2000. Exclusions: chronic course, no traceable history, DSM-IV Axis I comorbidity, or clinical/laboratory indications of severe organic disease	DSM-III-R/ DSM-IV	155	373
Stallone et al, 1980, United States[58]	5	Primary affective disorder patients attending clinic. Results for bipolar patients reported separately	Feighner	55	102
Tondo et al, 1999, Italy[59]	5	Inpatients and outpatients with major affective disorders seen between 1979 and 1998. Results for bipolar patients reported separately	DSM-IV	41	337
Tsai et al, 1999, Taiwan[30]	4	Bipolar patients recruited 1995–1996; inclusions: treated for at least 15 y with at least 30 follow-up visits	DSM-III-R	53	48
Uçok et al, 1998, Turkey[60]	5	Bipolar I outpatients attending clinic between Oct 1995 and March 1996	DSM-III-R	19	71
Vieta et al, 1997, Spain[31]; Vieta et al, 2001, Spain[34,d]; Vieta et al, 2000, Spain[33,d]; Vieta et al, 1999, Spain[32,d]	4	Bipolar (I or II) outpatients attending clinic, age 18–65 y	RDC	18	42
Wu and Dunner, 1993, United States[61]	5	Bipolar outpatients who presented between 1989 and 1992	DSM-III-R	72	148
Young et al, 1993, Canada[62]	5	Bipolar (I or II) outpatients consecutively treated in clinic	RDC	20	61

[a]1 = prospective cohort, 4 = cross-sectional case-control, 5 = cross-sectional case-control (lifetime history of attempted suicide).
[b]Subjects and controls, source, date of recruitment, follow-up period, important exclusion criteria, other details.
[c]Bipolar disorder only unless otherwise stated.
[d]Report from the same study usually including a smaller and/or overlapping subject sample or shorter follow-up period.
Abbreviations: NIMH = National Institute of Mental Health, NOS = not otherwise specified, RDC = Research Diagnostic Criteria, SADS = Schedule for Affective Disorders and Schizophrenia, lifetime version.

Figure 1. Suicide and Demographic Characteristics of Patients With Bipolar Disorder



[a]1 = prospective cohort, 2 = retrospective cohort, 3 = case-control.

The number of studies in the different categories was as follows:

Suicide. (1) Prospective cohort, 4 studies[10–17]; (2) retrospective cohort, 5 studies[18–23]; (3) case-control study, 4 studies.[24–27]

Attempted suicide. (1) Prospective cohort, 1 study[14–16,28,29]; (2) retrospective cohort, 0 studies; (3) case-control study, 0 studies; (4) cross-sectional case-control study, 2 studies[30–34]; (5) cross-sectional case-control study (lifetime history), 20 studies.[20,35–62] In addition, data from Endicott et al.[63] are included here, that study being included in Coryell et al.[14–16,28,29] Some single studies were reported in multiple articles.

Risk Factors for Suicide

Sociodemographic factors (Figure 1). Suicide risk was associated with male gender. It was not associated with racial origin (although there were only 2 studies that reported this factor[13,25]), marital status, or employment status.

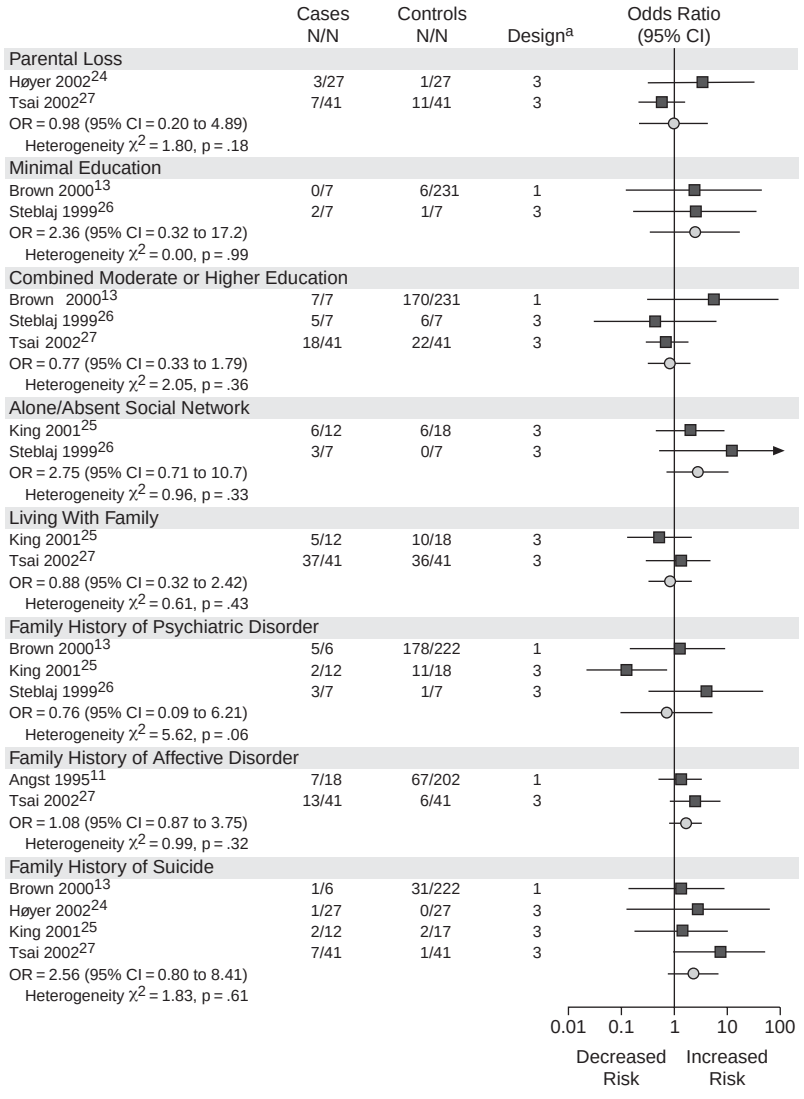
Personal, social, and family history (Figure 2). There were no statistically significant associations of suicide with personal, social, or family history characteristics. However, there was a nonsignificant trend toward an association with a family history of affective disorder (2 studies[11,27]) and a family history of suicide (4 studies[13,24,25,27]).

Clinical characteristics (Figure 3). Suicide risk was associated with a history of attempted suicide. On the basis of the results of 2 relatively small investigations,[25,26] it was also associated with patients having expressed hopelessness at the index admission (i.e., the admission that brought them into the study). Suicide risk did not seem to vary according to whether an individual had a diagnosis of bipolar I or bipolar II disorder, but there were relatively little data on this. Nor was there an association with depression diagnosed on the index admission, although an association was reported in 1[18] of the 2 studies[18,25] included in this part of the analysis. There was no association between suicide and rapid cycling of bipolar disorder, nor with whether individuals had suffered psychotic disorder during their illness. Neither was suicide associated with alcohol abuse, drug abuse, alcohol and/or drug abuse, insomnia, expression of suicidal ideas, or having a history of compulsory admissions. However, for each of these variables, there were only 2 studies available for analysis.

Risk Factors for Attempted Suicide or Deliberate Self-Harm

Sociodemographic and family characteristics (Figure 4). Nonfatal suicidal behavior was not associated with gender, although there was substantial heterogeneity in the overall result. Attempted suicide was significantly more common in single individuals. There was a clear as-

Figure 2. Suicide and Personal, Social, and Family Characteristics of Patients With Bipolar Disorder



[a]1 = prospective cohort, 3 = case-control.

sociation with a family history of suicide. Attempted suicide was not associated with a family history of affective disorder, unemployment, or living alone (although few studies examined these factors).

In a single but relatively large study[48] (study design 5), attempted suicide was associated with a history of early physical abuse (90/219 cases [41.1%] vs. 94/429 controls [21.9%]; OR = 2.49, 95% CI = 1.72 to 3.60) and early sexual abuse (90/219 cases [41.1%] vs. 99/429 controls [23.1%]; OR = 2.33, 95% CI = 1.61 to 3.35).

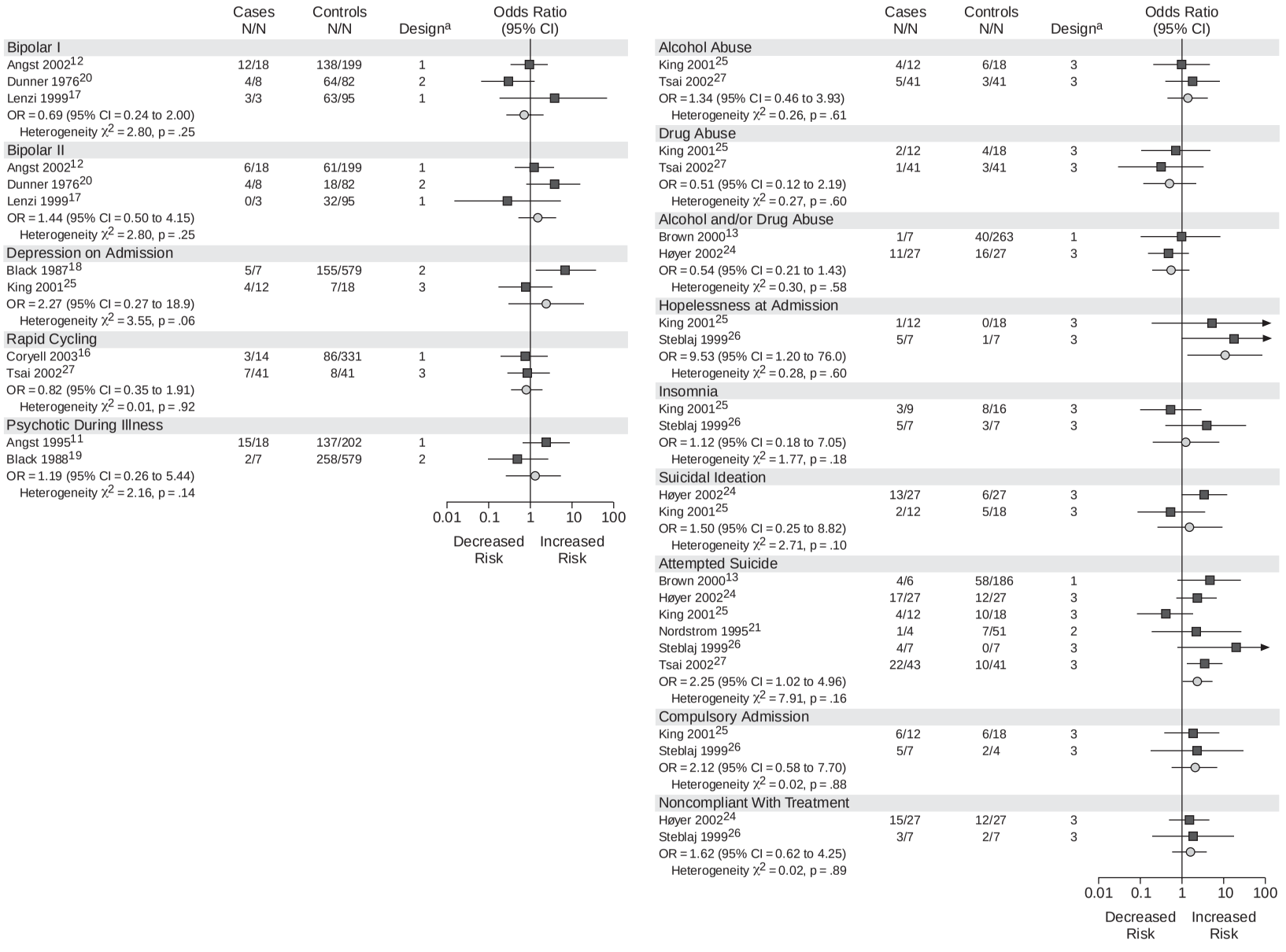
Clinical characteristics (Figure 5). On the basis of consistent findings across 5 studies[30,35,40,48,49] (results not shown in figure), attempted suicide was more common the earlier the onset of bipolar disorder (weighted mean difference = –2.97 years, 95% CI = –4.54 to –1.40; heterogeneity χ^2 = 6.39, p = .172). Attempted suicide did not appear to be associated with a diagnosis of bipolar I disorder. There was a trend toward an association with bipolar II disorder, but this did not reach significance (although there was heterogeneity in the result). On the basis of the findings of just 2 studies,[40,48] attempted suicide was strongly associated with admission to hospital resulting from depression. Conversely, on the basis of 2 studies, there was a negative association with mania at the time of hospitalization, which resulted in the patients entering the study. However, the results of a single but large study[48] (study design 5) showed an association between a history of attempted suicide and increasing severity of both depressive episodes (137/219 cases [62.6%] vs. 230/429 controls [53.6%]; OR = 1.45, 95% CI = 1.02 to 2.05) and manic episodes (121/219 cases [55.3%] vs. 180/429 controls [42.0%]; OR = 1.71, 95% CI = 1.21 to 2.40). Mixed affective states at presentation were related to attempted suicide risk, although this was only investigated in 3 studies. Attempted suicide was also associated with a diagnosis of rapid cycling disorder. Although there was significant variation between the findings of the studies, a positive finding occurred in the study with the strongest design.[16]

Attempted suicide was associated with comorbid anxiety disorder. It was also clearly linked to substance misuse, there being a significant association with alcohol abuse, drug abuse, and the presence of either or both of these. In a single (study design 5) study,[48] attempted suicide was associated with comorbid eating disorder (28/122 cases [23.0%] vs. 29/258 controls [11.2%]; OR = 2.35, 95% CI = 1.28 to 4.33).

DISCUSSION

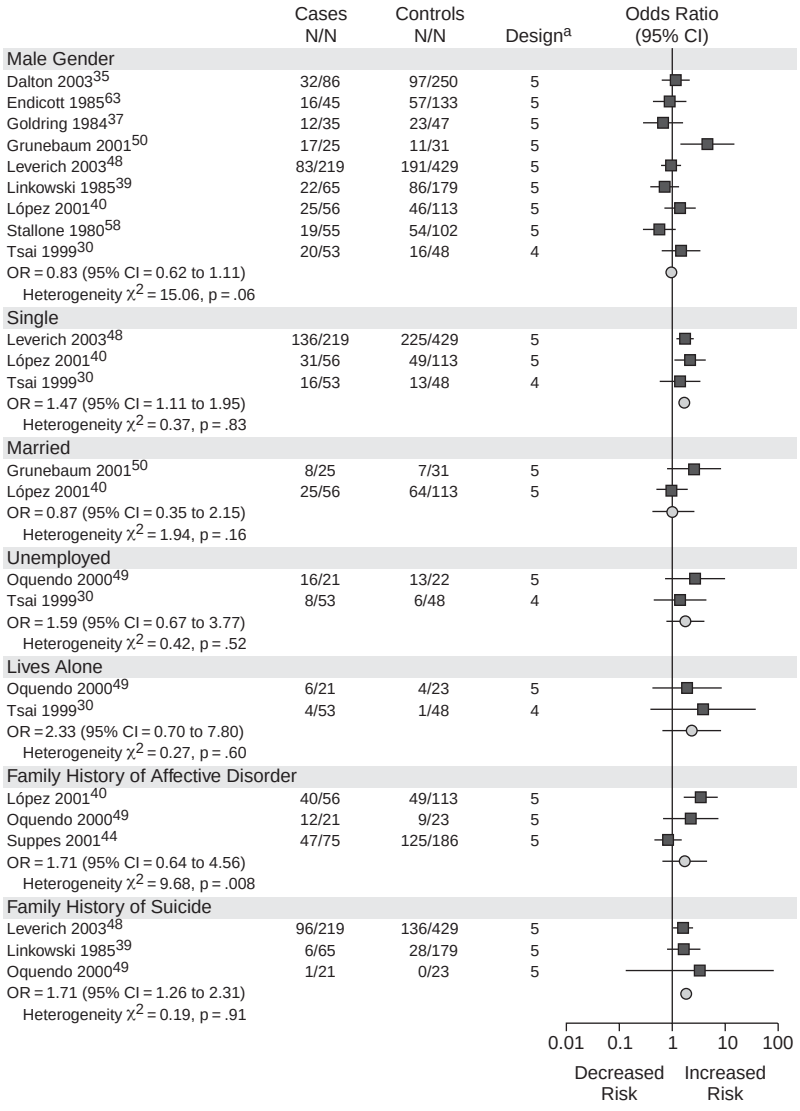
The risk of suicide in bipolar disorder is extremely high, and nonfatal suicidal acts occur in many patients.[1] Ongoing assessment of risk of suicidal behavior should be an integral part of the management of patients with bipolar disorder. The results of this systematic review and meta-analysis may assist clinicians in this task because they provide evidence of risk factors synthesized from the results of multiple investigations. Thus clinicians can

Figure 3. Suicide and Clinical Characteristics of Patients With Bipolar Disorder



[a]1 = prospective cohort, 2 = retrospective cohort, 3 = case-control.

Figure 4. Attempted Suicide and Sociodemographic and Family Characteristics of Patients With Bipolar Disorder



[a]4 = cross-sectional case-control, 5 = cross-sectional case-control (lifetime history of attempted suicide).

consider these with some confidence when assessing patients for risk of suicidal acts. They can also use the findings in discussing risk with relatives.

Factors Associated With Risk of Suicide

Relatively few variables were identified as risk factors for suicide when data from different studies were combined. However, for many of the variables examined there was a paucity of data, which in part reflects the low base rate for suicide. As in the general population, suicide was more frequent in males, although the relatively low gender ratio as reflected in the overall odds ratio was somewhat lower than is usually found for suicide. This finding suggests that the relative suicide potential in females with bipolar disorder is not so very different from that in males. In contrast to suicides in the general population, there was no apparent association of suicide with marital or employment status or with early loss or social isolation.

Very few studies have examined how family history of affective disorder or suicidal behavior might contribute to suicide risk in bipolar disorder patients, which may explain the lack of association found in the meta-analyses. Generally, studies of suicides have indicated that a family history of suicidal behavior increases suicide risk in people with psychiatric disorders, irrespective of the diagnosis.[64]

A lack of association of suicide with clinical characteristics of the disorder, including the bipolar II subtype, psychotic symptoms, or rapid cycling, may also reflect the small number of studies in which these factors were examined. It has been suggested that both suicide and attempted suicide are more common in bipolar II disorder than in bipolar I disorder.[5] In keeping with this claim, we found a lower risk of suicide in patients with a diagnosis of mania at their index hospitalization (presumably bipolar I patients). A paucity of studies may have undermined the results for drug and alcohol abuse and for insomnia and suicidal ideation. The main findings of the meta-analyses were that suicide risk appeared to be elevated where there was a history of attempted suicide and, probably, hopelessness. Both attempted suicide[65] and hopelessness[66] are strongly linked to suicide risk in general.

Factors Associated With Risk of Attempted Suicide

Rather more factors were found to be associated with nonfatal suicidal behavior, in part because this behavior is far more frequent than suicide. Also, most of these studies were of a relatively weak cross-sectional retrospective design, in which a wide range of factors are more easily examined than in prospective studies.

The lack of an association with female gender contrasts markedly with the picture for attempted suicide in general.[67] Again, this may indicate that bipolar disorder increases the risk for suicidal behavior to a similar degree in both sexes. The association with single marital status is the same as found in the general population. Findings

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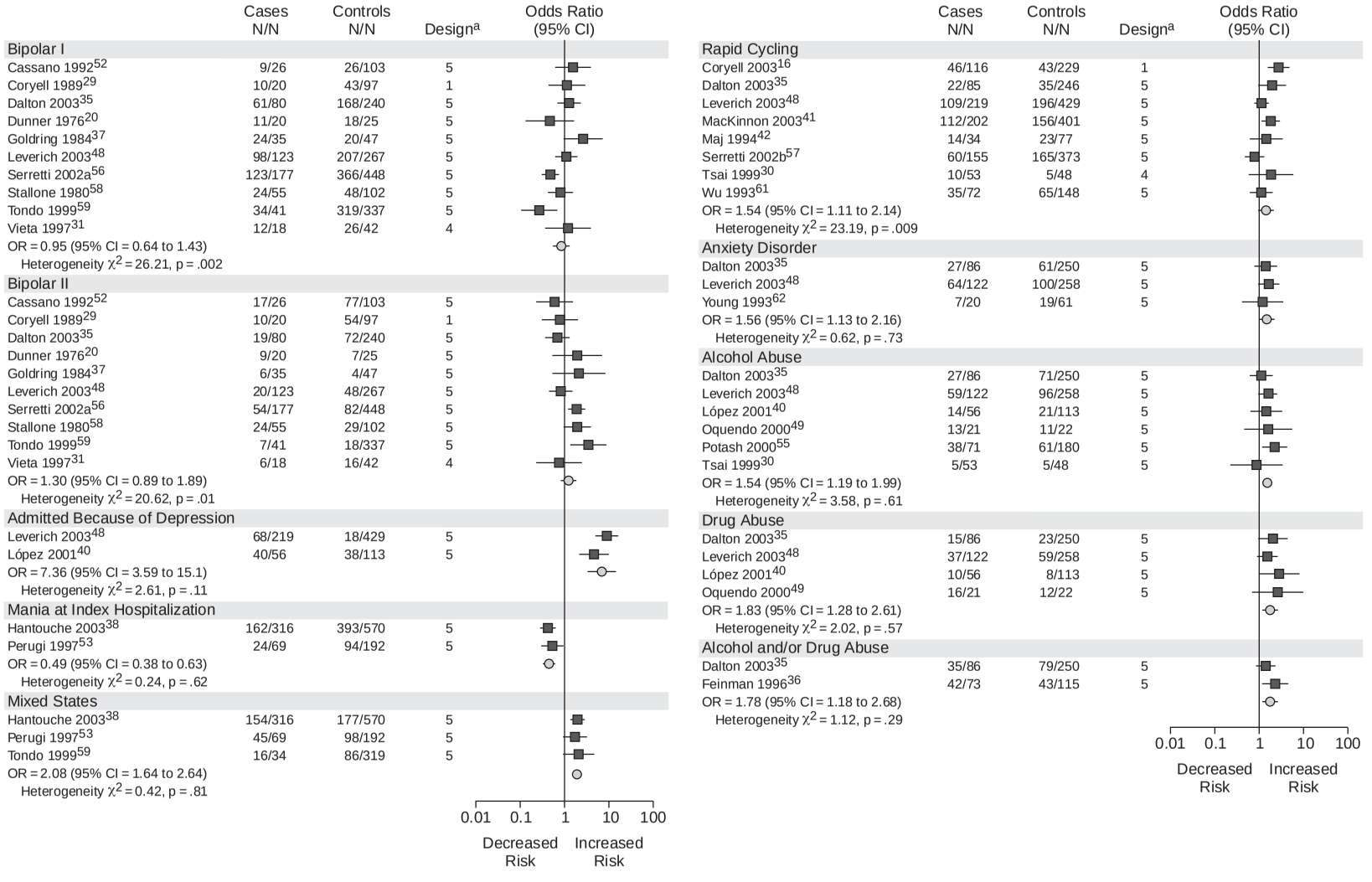
Figure 5. Attempted Suicide and Characteristics of Bipolar Disorder



[a]1 = prospective cohort, 4 = cross-sectional case-control, 5 = cross-sectional case-control (lifetime history of attempted suicide).

from a single study linked attempted suicide in bipolar disorder patients with early experiences of both physical and sexual abuse, which are both factors known to be associated with self-harming behavior in general.[46] Family history of suicide increased the risk of attempted suicide in bipolar disorder.

There were clear associations of nonfatal suicidal behavior with specific characteristics of bipolar disorder. These included earlier onset of the disorder and a preponderance of depressive symptoms. Risk of attempted suicide also appeared to be increased in patients with a diagnosis of rapid cycling and those with mixed affective states. On the basis of the findings of a single but large retrospective study,[48] attempted suicide is associated with increasing severity of affective episodes.

Comorbidity with drug and alcohol abuse increased risk of attempted suicide in bipolar disorder, as is found in other psychiatric disorders.[68] Risk was also increased when there was comorbid anxiety or eating disorders.

Methodological Issues

As in all systematic reviews, there may be a bias toward studies with positive results because of a greater likelihood of these being reported and published. Some potential risk factors have been subjected to considerable scrutiny; others have been investigated in very few studies, and the results for these factors must be considered with greater uncertainty. The definition of some of the potential risk factors differed between studies, which inevitably means that there was some compromise over the specificity of definition of items in order to allow inclusion of the largest possible number of studies.

The advantage of meta-analysis of summary data is that it allows the results of a large range of studies to be synthesized, reduces the danger of data from individual studies leading to spurious conclusions, and provides findings weighted by the strength of study design. A disadvantage of this approach, however, is that it is not possible to adjust the estimates of risk factors for the confounding effects of other variables (which would require having access to individual patient data).

Clinical and Research Implications

Bipolar disorder markedly enhances risk of suicidal behavior in both genders. The main factor that increases risk of suicide is a previous suicide attempt. This strong association means that the clinician can reasonably extrapolate from the findings of factors associated with nonfatal acts when considering other characteristics relevant to risk of suicidal behavior in general in bipolar disorder. Other factors that are therefore important to include in assessment of risk are family history, especially of suicide, a history of abuse, early age at onset of bipolar disorder, extent of depressive symptoms (especially hopelessness), increasing severity of affective episodes, the presence of mixed affective states, rapid cycling, comorbid Axis I disorders, and abuse of alcohol or drugs.

Given the strong association between bipolar disorder and suicidal behavior, there is a need for more large-scale prospective studies of risk factors for both suicide and attempted suicide in individuals with this condition. Increasing evidence that lithium may have a specific antisuicidal effect[3] should encourage such investigations. Future studies should address psychological and personality factors as well as those included in the studies identified in this review. The findings of such research may enhance the ability of clinicians to detect individuals at risk and institute preventative therapeutic interventions.

Drug name: lithium (Eskalith, Lithobid, and others).

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