Illness Progression as a Function of Independent and Accumulating Poor Prognosis Factors in Outpatients With Bipolar Disorder in the United States

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ABSTRACT

Objective: Many patients with bipolar disorder in the United States experience a deteriorating course of illness despite naturalistic treatment in the community. We examined a variety of factors associated with this pattern of illness progression.

Method: From 1995 to 2002, we studied 634 adult outpatients with bipolar disorder (mean age of 40 years) emanating from 4 sites in the United States. Patients gave informed consent and completed a detailed questionnaire about demographic, vulnerability, and course-of-illness factors and indicated whether their illness had shown a pattern of increasing frequency or severity of manic or depressive episodes. Fifteen factors previously linked in the literature to a poor outcome were examined for their relationship to illness progression using Kruskal-Wallis test, followed by a 2-sample Wilcoxon rank sum (Mann-Whitney) test, χ^2, and logistical regression.

Results: All of the putative poor prognosis factors occurred with a high incidence, and, with the exception of obesity, were significantly ($P < .05$) associated with illness progression. These factors included indicators of genetic and psychosocial risk and loss of social support, early onset, long delay to first treatment, anxiety and substance abuse comorbidity, rapid cycling in any year, and the occurrence of more than 20 prior episodes prior to entering the network. A greater number of factors were linearly associated with the likelihood of a progressively worsening course.

Conclusions: Multiple genetic, psychosocial, and illness factors were associated with a deteriorating course of bipolar disorder from onset to study entry in adulthood. The identification of these factors provides important targets for earlier and more effective therapeutic intervention in the hope of achieving a more benign course of bipolar disorder.

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While many patients with bipolar disorder respond well to treatment, an increasingly large group have not only continuing difficulty, but also a course of illness characterized by increasing frequency or severity of manic or depressive episodes or what could be considered a pattern of illness deterioration or progression. We assessed the relationship of a host of factors that have previously been associated with a poor outcome in bipolar disorder to several patient-rated measures of illness progression that occurred prior to entry in our network in outpatients from the United States.

In the United States, the prevalence of bipolar disorder is in the range of 3%–5%,[1]and, in primary care, 9.8% of patients screened positive for bipolar disorder, but few were taking mood stabilizers or had a bipolar diagnosis entered into the record.[2] Even in patients who were given a new diagnosis of bipolar disorder in another study,[3] 50% were treated with antidepressants, mostly in monotherapy (which is not recommended), and much fewer numbers of patients were treated with approved classes of medications such as lithium, mood stabilizers, or atypical antipsychotics.

The problem of poor recognition and treatment of bipolar disorder is particularly acute in the United States, where virtually every aspect of the illness is more difficult or severe than in European countries such as the Netherlands or Germany.[4,5] These difficulties include more genetic vulnerability (parents and grandparents with bipolar and other illnesses), psychosocial stressors in childhood and over the course of illness, childhood onset (ie, 31% before age 13 and 69% before age 19 years), anxiety and substance comorbidity, manic and depressive episodes and rapid cycling, treatment nonresponse, and medical comorbidities. Childhood onset of bipolar disorder is associated with long delays to first treatment and a difficult course of illness into adulthood.[6,7]

Factors that had been previously associated in the literature and in our own studies with an adverse course of bipolar disorder were examined and included a history of childhood adversity (verbal, physical, or sexual abuse); early age at onset (prior to age 19 years); delay to first treatment for a manic or depressive episode; a history of anxiety or substance abuse comorbidity; rapid cycling; 20 or more prior episodes of depression or mania, being overweight (body mass index [BMI, kg/m^2] > 26), having more than 2 medical comorbidities; poor social support, poor health care access; and employment difficulties.[8] We wanted to see which of these factors individually and as a group might be associated with illness progression despite treatment in the community so that greater clinical attention could be paid to these factors and their amelioration. We postulated that each of these poor prognosis factors and the total number of them would be associated with a greater likelihood of a progressively worsening course of bipolar disorder.

Clinical Points

- Bipolar illness in the United States is common, exceedingly complicated, often progressive, and in need of careful screening and follow-up.
- A variety of vulnerability and poor prognosis factors occur in a high proportion of US patients and are thus targets for early and concerted treatment; these include childhood adversity; early onset of bipolar disorder in childhood or adolescence in two-thirds of outpatients; more anxiety, substance abuse, and medical comorbidity; more episodes and rapid cycling; and more treatment resistance.
- Screening, treatment or referral, and careful longitudinal follow-up of manic and depressive symptoms and of comorbid medical conditions may help avert the very high incidence of illness progression and a poor long-term outcome of bipolar disorder in patients in the United States.

METHOD

We examined self-reports of illness course and poor prognosis factors in 634 adult outpatients with bipolar disorder (mean age of 40 years) emanating from 1 of 4 sites in the United States, which included Los Angeles, California; Dallas, Texas; Cincinnati, Ohio; and Bethesda, Maryland. Patients gave verbal and written consent for participation in what was then called the Stanley Foundation Bipolar Network (1995–2002) and now continues as the Bipolar Collaborative Network.[9–11]

Given the international differences in the degree of treatment resistance and the very considerable differences in risk factors, age at onset, comorbidities, and course of illness variables in patients from the United States versus those from Europe,[11–14] we examined the impact of the poor prognosis factors on illness progression only in the US patients in order to avoid the many clinical and statistical confounds that would be present in a divergent combined population.

The measures of illness progression/deterioration were taken from a questionnaire filled out by patients at network entry who answered "probably" or "definitely" to 3 questions on whether their illness was characterized by an increasing (1) severity of depression, (2) severity of mania, or (3) frequency of episode occurrence.

The poor prognosis factors examined included a childhood history of physical/sexual abuse, verbal abuse in childhood, onset of illness prior to age 19 years, delay to first treatment of more than 4 years, a lifetime history of anxiety or substance abuse comorbidity, rapid cycling, ≥20 prior episodes of mania and depression, a BMI (>26) reflecting overweight or obesity, the experience of more than 2 medical comorbidities (from a list of 14 potential illnesses), poor social support (taken as a moderate or greater rating of lack of support on questions about a spouse, a confidant, the family, or the social network), poor health care access (moderate or greater difficulties with health care coverage or access), and employment difficulties (moderate or greater).[6,15–17]

Statistics

The influence of the putative poor prognosis factors on a deteriorating illness course was examined with a Kruskal-Wallis test, followed by a 2-sample Wilcoxon rank sum (Mann-Whitney) test. The relationship to illness progression of isolated vulnerability factors and other course-of-illness variables was evaluated with Person's χ^2. The independent contribution of the poor prognosis factors was assessed by linear regression analysis. This analysis was performed for each of the 3 measures of illness deterioration/progression separately, but reported in detail only for the combined measure of any evidence of illness deterioration based on a positive answer to any 1 of the 3 questions on the increasing severity of manic or depressive episodes or their increasing frequency of occurrence.

RESULTS

Table 1 lists the high incidence of each of the putative poor prognosis factors in this population of outpatients in the United States with bipolar illness. Each of these poor prognosis factors (with the exception of overweight/obesity) occurred in a higher percentage of patients who had a deteriorating course of illness compared to those who did not progress (Table 2) when any of the 3 measures of increasing frequency or severity of mania or depression were used. These poor prognosis factors consistently occurred in 78%–84% of patients who had illness progression, but in only 50%–70% of the patients without illness progression.

In the 3 columns on the right side of Table 2 are the significant relationships of each factor to the 3 measures of illness progression separately, ie, increasing severity of depression, increasing severity of mania, or increasing frequency of episode occurrence. As all of these relationships were in a similar range of statistical significance, we chose to present the percentages and χ^2 values only for the single combined measure of illness progression on any 1 of the 3 measures.

As illustrated in Figure 1, those with a greater number of poor prognosis factors showed an increasing likelihood of illness progression ($n = 657$, $\chi^2 = 113.15$, pseudo $R^2 = 0.152$, $P < .001$). This relationship rose fairly linearly with increasing number of factors from 0 to 8 and then gradually leveled off, such that those with 9 to 14 poor prognosis factors were 85%–90% likely to show a pattern of illness worsening prior to network entry.

When the independent contribution of each of the poor prognosis factors to illness progression was evaluated in a logistic regression (Table 3), the occurrence of rapid cycling remained highly significant, while early age at onset, substance abuse comorbidity, and a delay to first treatment of ≥4 years were at a trend level. These relationships were generally parallel to the magnitude of the χ^2 values observed in the univariate analysis (Table 2).

DISCUSSION

These data underscore the large variety of negative factors that might contribute to a pattern of increasing severity or

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Table 1. Measures of Illness Progression and Poor Prognosis Factors Present in a Large Portion of Patients With Bipolar Disorder in the United States

	Total N	Poor Prognosis Factor Present			
		n	%	SE	95% CI
Illness progression variables					
Increasing severity of depression	655	416	63.5	0.02	0.60–0.67
Increasing severity of mania	653	356	54.5	0.02	0.50–0.59
Increasing episode frequency	660	350	53.0	0.02	0.49–0.57
Any illness progression	661	492	74.4	0.02	0.71–0.78
Putative poor prognosis factors					
Parental history of depression	602	326	54.2	0.02	0.50–0.58
Parental history of bipolar disorder	587	213	36.3	0.02	0.32–0.40
Childhood physical or sexual abuse	647	261	40.3	0.02	0.37–0.45
Childhood verbal abuse	647	374	57.8	0.02	0.54–0.62
Early age at onset (before age 19 y)	652	452	69.3	0.02	0.66–0.73
Social stress at onset	662	453	68.4	0.02	0.65–0.72
Delay to treatment (≥ 4 y)	608	408	67.2	0.02	0.63–0.71
Anxiety disorder comorbidity	675	321	47.5	0.02	0.43–0.52
Substance abuse comorbidity	675	330	48.9	0.02	0.45–0.53
Rapid cycling (≥ 4 episodes/y)	637	471	73.9	0.02	0.70–0.77
> 20 Manic/depressive episodes	638	379	59.5	0.02	0.55–0.63
Body mass index (kg/m^2) > 26 overweight or obese	648	413	63.7	0.02	0.60–0.68
> 2 Medical comorbidities	668	298	44.6	0.02	0.41–0.49
Poor health care access	666	188	28.2	0.02	0.25–0.32
Employment difficulties	669	462	69.1	0.02	0.66–0.73

frequency of manic and depressive episodes despite how patients were treated in the community prior to network entry. Each factor has been previously linked to a more difficult course of illness in the literature,[8] and most of these individual factors were present in a substantial portion of about 40%–70% of the US patients. With the exception of obesity, the presence as opposed to the absence of each of these putative poor prognosis factors was significantly related to a deteriorating course of illness as rated at network entry.

There was also a strong relationship of the total number or accumulation of these poor prognosis factors to a progressively deteriorating course of illness in terms of increasing frequency or severity of manic and depressive episodes (as illustrated in Figure 1). Each additional poor prognosis factor appeared to further increase the likelihood of having a deteriorating course. If a patient had ≥ 9 of these poor prognosis factors, there was an approximate 85% likelihood that they showed a pattern of illness progression. Both the χ^2 in the univariate analysis and the logistic regression identified several of the poor prognosis factors as the most prominent contributors to the deteriorating course; these included a history of rapid cycling, an onset of illness in childhood or adolescence (prior to age 19 years), a > 4-year delay from illness onset to first treatment for either mania or depression, and a history of substance abuse comorbidity.

Childhood-onset, compared to adult-onset, bipolar disorder has been multiply associated with a more adverse course of illness.[6,7,18–22] This poor outcome makes sense, as the illness in children is difficult to treat and stabilize and is associated with a high rate of relapse, with children being symptomatic about two-thirds of the time during long-term prospective follow-up.[23–27] Thus, the occurrence of early illness, especially if it were not treated for an extended duration (at least 4 years), would negatively impact social, educational, and cognitive/emotional skills at important stages of development and be associated with the accumulation of mood episodes and psychosocial stressors, as well as the likelihood of substance abuse.[6,7,28] Early onset illness has consistently also been linked to a greater genetic vulnerability,[29] raising the possibility that early onset bipolar disorder is inherently more malignant than adult-onset bipolar disorder.

However, taken together, these findings are consistent with the view that stressors (both prior to and during the course of illness), episodes of illness, substance abuse, and a variety of other factors present in a high proportion of US patients contribute to the pattern of increasing severity/frequency of episodes of mania and depression. The repetition and recurrence of intermittent stressors, affective episodes, and bouts of substance use may cause not only an increase in the magnitude of behavioral response, reactivity, and pathology (ie, sensitization rather than tolerance), but also cross-sensitization to the others,[30,31] resulting in a potential vicious positive feedback cycle. For example, recurrent stressors may precipitate new affective episodes or the relapse of substance use, each of which could further engender new stressors, and so on.

The literature is replete with examples of how early life stressors may provide the basis of a lasting increased vulnerability to episode recurrence and potentially an increased responsivity or sensitization to later stressors in adulthood.[13,14,32–37] This increased vulnerability in those with childhood adversity to depression following the occurrence of new stressors in adulthood has been consistently demonstrated, even if a gene (such as the 5HT-T short allele)–environmental interaction is not always replicated.[32,36,38] Such persisting and sensitizing effects of early stressors might occur via epigenetic mechanisms as demonstrated in animals and humans.[31,39–46] Concurrent substance abuse has also been associated with a more difficult course of bipolar disorder,[47] and it too carries the potential for sensitization via epigenetic mechanisms and cross-sensitization to both stressors and episodes.[31]

The occurrence of multiple episodes and rapid cycling has similarly been associated with a more treatment-nonresponsive illness to a great many different treatment modalities.[30] A greater number of prior episodes has been independently linked to the vulnerability and latency to episode recurrence (a manifestation of episode sensitization),[34,48] as well as to cognitive deterioration.[30,49]

In addition, childhood stressors and greater numbers of mood episode can each exert diverse adverse psychiatric and medical effects because of an increased percentage of short telomeres and/or decreases in telomerase activity.[50–54]

Many other adversities and course-of-illness characteristics may also accumulate and further contribute to illness deterioration and magnify stressor burden, adversity, and demoralization. For example, having ≥ 2 medical comorbidities, unemployment difficulties, lack of health care access, and lack of social support have been

Table 2. Relationship of Poor Prognosis Factors to Patterns of Illness Progression[a]

Factor	% Illness Progression if Poor Prognosis Factor is Absent	% Illness Progression if Poor Prognosis Factor is Present	χ^2	*P*	*P* Depression	*P* Mania	*P* Episode Frequency
Childhood physical or sexual abuse	69.3	83.5	14.1	0	.01	0	0
Childhood verbal abuse	63.4	82.5	30.0	0	0	0	0
Early age at onset	58.9	81.1	35.5	0	0	0	0
Anxiety disorder	66.1	84.2	28.3	0	0	0	0
Substance abuse	67.8	81.8	16.9	0	0	0	.01
Rapid cycling	51.5	84.3	71.8	0	0	0	0
> 20 Episodes	60.2	85.6	53.6	0	0	0	0
Body mass index overweight or obese	76.0	73.2	0.6	.45	.21	.77	.88
> 2 Comorbidities	68.4	82.3	16.4	0	0	0	0
Social stress	67.5	78.1	8.3	0	.01	.32	0
Health care	70.8	83.9	12.0	0	.03	.01	0
Employment	65.7	78.6	12.3	0	0	0	0
Delay to treatment (≥ 4y)	56.1	82.8	49.6	0	0	0	0
Family history of depression	68.6	79.7	9.6	0	0	0	.04
Family history of bipolar disorder	72.3	80.2	4.5	.03	.19	.04	0

[a]The second column of numbers indicates the % of patients who have a pattern of illness progression if that putative poor prognosis factor is absent (first column) or if it is present (third column); χ^2 is in the next column, with statistical significance in the next. The last 3 columns indicate the significant relationship of each variable to a given pattern of illness progression evident in increasing severity of depression, severity of mania, or frequency of recurrence of episodes, respectively. As the relationships are similar to the other measure of any type of illness progression, the χ^2 values are not presented for each individual measure. A *P* value of zero equals $P < .001$.

Figure 1. More Poor Prognosis Factors Associated With Greater Illness Progression

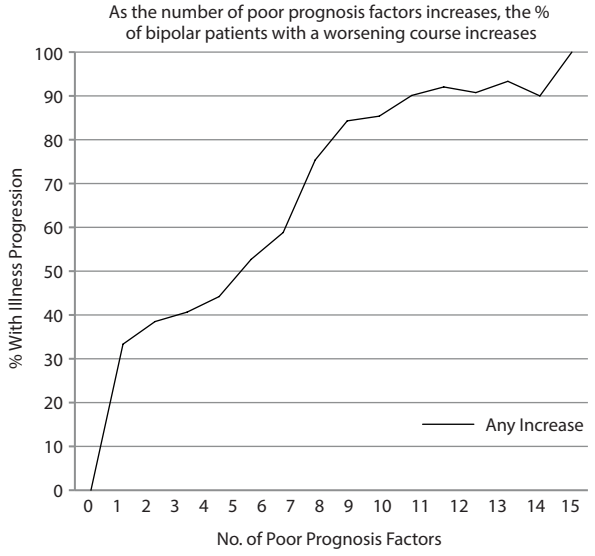

Table 3. Multivariate Analysis of Independent Contributors to Illness Progression[a]

Variable	Odds Ratio	SE	*z*	*P*	95% CI
Physical or sexual abuse	1.11	0.32	0.38	.71	0.63–1.96
Verbal abuse	1.35	0.38	1.07	.28	0.78–2.34
Age at onset	1.62	0.44	1.80	.07	0.96–2.75
Anxiety disorder	1.36	0.36	1.19	.23	0.82–2.27
Substance abuse	1.57	0.40	1.80	.07	0.96–2.58
Rapid cycling	2.80	0.80	3.61	0	1.60–4.91
> 20 Episodes	1.46	0.42	1.32	.19	0.83–2.58
Body mass index (kg/m^2) > 26	0.92	0.23	0.34	.73	0.56–1.51
> 2 Comorbidities	1.22	0.32	0.77	.44	0.73–2.03
Poor social support	1.18	0.31	0.63	.53	0.71–1.97
Poor health care	1.32	0.41	0.91	.36	0.72–2.42
Poor employment	1.32	0.35	1.05	.3	0.79–2.21
Family history of depression	1.18	0.30	0.65	.52	0.72–1.94
Family history of mania	0.95	0.26	0.19	.85	0.55–1.63
Delay to treatment > 3 y	1.65	0.45	1.85	.07	0.97–2.82

[a]A logistic regression found poor prognosis factors successfully predicted illness progression (likelihood ratio $\chi^2 = 96.46$, $P < .001$, pseudo $R^2 = 0.1809$, n = 480). A *P* value of zero equals $P < .001$.

associated with an increased incidence of suicide attempts in patients with bipolar disorder,[16,55] and each of these difficulties occurs in more than 50% of these patients from the United States. Having an anxiety disorder comorbidity has also consistently been associated with a poor outcome in patients with bipolar disorder.[30,56]

Clearly, those with a prior deteriorating course of bipolar illness have a greater number of these varied problems than those whose illness did not progress in this negative direction. Being overweight or obese by BMI measurement, even though it was not related to our indices of illness progression, has also been associated with other measures of a poor outcome in bipolar disorder,[57] including cognitive difficulties and the accumulation of further medical comorbidities.

Limitations

A number of limitations need to be considered in the interpretation of these findings. All of the data are retrospective and based on patient self-report. The assessment of the main outcome measure of a progressive/deteriorating course of illness based on the report of an increasing frequency or severity of episodes of mania or depression is to some extent subjective and may not correlate highly with other more quantitative measures of poor outcome such as more time ill, less time euthymic, or more hospitalizations.

Some of the poor prognosis factors considered, such as rapid cycling or having had ≥ 20 prior episodes, may be intertwined with the definition of illness progression in terms of increasing frequency of episodes. However, it is also possible for patients to experience periods of rapid cycling or a high density of episodes and then respond well

to treatment and show improvement or remission,[8,10,58–60] so that these variables are not inextricably confounded. Also, the variables we chose to examine as likely poor prognosis factors from the literature do not represent an exhaustive list, and many other potential contributors to illness progression could also have been studied.

The findings are based on data exclusively from patients in the United States, and their generality to other populations and countries may not be warranted.[4] A major limitation is that type and intensity of pharmacologic, somatic, and psychosocial treatment that patients received in the community prior to network entry was not accounted for. However, other measures of illness progression in the literature, such as the likelihood of episode recurrence as a function of the number of prior episodes, also were highly significant when the potential effects of treatment were not taken into account.[61] Finally, more sophisticated modeling of causal mechanisms and sequences could not be performed, as the details and time of occurrence of the poor prognosis factors were not available.

Clinical and Public Health Implications

Despite these limitations, the findings identify a host of commonly occurring demographic, psychosocial, and illness characteristics associated with a pattern of illness progression or deterioration that was reported in more than two-thirds of the outpatients with bipolar disorder from the United States in our network. This result suggests that bipolar disorder as characterized in this population was in general poorly responsive to conventional treatment received in the community in a very high proportion of patients prior to network entry. These data converge with those in many other populations, indicating that bipolar disorder in the United States as it is currently treated both in children[25–27,62] and in adults[18,63–65] is characterized by an extraordinarily high degree of treatment resistance.

Many of the variables previously associated with a poor outcome in the literature and with illness progression in this study were present in a high proportion of our patients from the United States, and, thus, each potentially represents an important target for therapeutic intervention. There perhaps is little one can do presently about genetic vulnerability and a parental diagnosis of a mood disorder or an early onset of illness, but more rapidly instituting appropriate treatment as the illness emerges[17] might render the illness more benign, especially since the duration of delay to first treatment is a contributor to a poor outcome,[6,19,22,66] even independent of the adverse course associated with early onset.[6]

The research groups of Chang et al[67] and Miklowitz et al[68,69] have shown that family-focused therapy for children at high risk (by virtue of both having a relative with bipolar disorder and having a prodromal diagnosis of an anxiety or depressive disorder or bipolar disorder not otherwise specified) is associated with considerable improvement on a variety of measures compared to treatment as usual. Thus, family-focused therapy or related psychosocial interventions in conjunction with pharmacotherapy could help head off many of the difficulties identified here, particularly in the realm of recurrence and accumulation of stressors, episodes, and substance use. Family-focused therapy focuses on enhancing communication, social support, and symptom identification and monitoring, and these approaches could contribute to decreasing the incidence of verbal and emotional abuse and more rapidly attenuating anxiety disorder comorbidity.

In children at high risk by virtue of having a parent or first-degree relative with bipolar disorder, there appears to be a fairly consistent sequence of emerging diagnoses starting first with an anxiety disorder in childhood, then depression, and then much later bipolar disorder in adolescence or adulthood.[70–73] In high-risk children in the United States, this progression of symptoms and diagnoses may be compressed or accelerated, with mania emerging earlier in childhood or adolescence in a more substantial percentage.[74–78] Thus, psychotherapeutic approaches, such as family-focused therapy, and appropriate pharmacotherapy of these early appearing syndromes would seem especially important. Attempting to achieve primary or secondary prevention of substance abuse in adolescents at such high risk by virtue of their bipolar disorder[79] should also be a consistent therapeutic endeavor. Thus, children at high risk of a mood or anxiety disorder by virtue of a parent with bipolar disorder should be carefully followed and treated and/or referred for psychiatric evaluation and treatment. If such a child has experienced verbal or other types of abuse, psychotherapy should also be considered, as this is an additional risk factor for not only early onset and more severe course of bipolar disorder, but also increases in a large array of medical illnesses in adolescence and adulthood.[13,35] One can have parents of children rate depressive, anxiety, posttraumatic stress disorder, and bipolar symptoms longitudinally on instruments such as My Mood Monitor (www.whatsmym3.com) or on a personal calendar available at www.bipolarnews.org, which is a newsletter that also carries the latest information on treatment and research for physicians, patients, and family members.

Primary care physicians also have a critical role in the treatment of the medical comorbidities that so often accompany bipolar disorder. Some 40% of patients in the United States have metabolic syndrome, and monitoring and treatment of elevated lipids, blood pressure, waist circumference, and blood sugar will play an important role in reducing the 1 to 2 decades of lost life expectancy mainly from cardiovascular disease in those with bipolar disorder and related major psychiatric illness.[80,81]

Given the high prevalence of so many poor prognosis factors in outpatients with bipolar disorder in the United States and the very high rates of treatment resistance reflected in the measure of illness progression/deterioration and in many other measures,[6,7,10,18,82] it would appear appropriate to reconceptualize the onset of bipolar disorder, particularly in childhood or adolescence, as a genuine medical emergency deserving the highest levels of both acute and long-term integrated and multimodal care (similar to that consistently

given for childhood-onset diabetes). The importance of special and intensive follow-up care in bipolar disorder is also demonstrated by Kessing et al[83] in their randomization of those with a first hospitalization for mania to either a specialty clinic (emphasizing illness education, monitoring, and early intervention) for 2 years or treatment as usual. Not only were there significantly few rehospitalizations in the specialty clinic group, but the differences between groups persisted and grew larger over the next 6 years (even though the specialty clinic treatment ended at 2 years).[83] Without new approaches to the complexity and multiplicity of factors associated with a deteriorating course of bipolar disorder in the United States, the illness is likely to continue to rob overwhelming numbers of patients of their medical and psychiatric health and well-being.

Drug names: lithium (Lithobid and others).

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