Bipolar Disorder: New Perspectives in Health Care and Prevention

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Objective: High rates of misdiagnosis, delayed diagnosis, and lack of recognition and treatment of comorbid conditions often lead patients with bipolar illness to have a chronic course with high disability, unemployment rates, and mortality. Despite the recognition that long-term outcome of bipolar disorder depends on systematic assessment of both interepisodic dysfunctional domains and comorbid psychiatric and medical conditions, treatment of bipolar disorder still focuses primarily on alleviation of acute symptoms and prevention of future recurrences. We propose here to review the evidence offering a modern view of bipolar disorder defined as a chronic and progressive multisystem disorder, taking into account characteristics of each patient as well as biosignatures in order to help design personalized treatments.

Data Sources: We conducted a systematic PubMed search of all English-language articles, published between 2000 and 2010, focusing on the English and French literature with *bipolar disorder* cross-referenced with the following search terms: *emotional dysregulation, sleep and circadian rhythm disturbances, cognitive impairment, age at onset, comorbid medical and psychiatric conditions, psychosocial and medical interventions, outcome, remission,* and *personalized medicine.* The search was conducted between July 2009 and July 2010. The literature on bipolar disorder was reviewed to provide supporting evidence that the assessment of various symptom domains that are dysfunctional between episodes should all be considered as core dimensions of the disorder.

Study Selection: Forty-one articles were identified through the PubMed search described above and selected on the basis of addressing any combination of the search terms in conjunction with bipolar disorder.

Data Synthesis: Current guidelines advocate the use of more or less similar treatment algorithms for all patients, ignoring the clinical, pathophysiological, and lifetime heterogeneity of bipolar disorder. Systematic assessment of interepisodic dimensions, along with comorbid medical and psychiatric risk factors, should be performed along the life cycle in order to plan specific and personalized pharmacologic, medical, and psychosocial interventions tailored to the needs of each patient and ready-to-test biosignatures to serve as risk factors or diagnostic or prognostic tools.

Conclusions: Medical and research findings, along with health economic data, support a more modern view of bipolar disorder as a chronic, progressive, multisystem disorder. This new comprehensive framework should guide the search to identify biomarkers and etiologic factors and should help design a new policy for health care, including prevention, diagnosis, treatment, and training.

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A ccording to the World Health Organization, bipolar disorder is the sixth cause of disability-adjusted life-years among all diseases.¹ In addition to the traditional bipolar I subtype, defined by episodes of mania and depression, the bipolar II subtype, with less severe hypomania and major depression, as well as bipolar spectrum subtypes bring its prevalence to 4.4% of the population.² These estimates are somewhat conservative, as elevated rates of misdiagnosis from 30% to 69% have been estimated in Europe and in the United States.^{3,4}

Bipolar disorder has been classically described as a cyclical illness, with full-blown manic or depressive episodes interspaced with normal euthymic periods. This traditional view needs to be changed, as evidence now suggests that patients experience a more subtle chronic course than initially thought, characterized by residual symptoms, emotional dysregulation, sleep and circadian rhythm disturbances, cognitive impairment, and increased risk for psychiatric and medical comorbidity between mood episodes. This revised view should not only promote the development of better diagnostic tools to allow a comprehensive clinical assessment but should also influence therapeutic strategies with targeted interventions designed to treat each of these interepisodic dimensions and risk factors in order to obtain better longterm prognoses. Greater awareness of the medical burden associated with bipolar disorder calls for an integrated medical care model. Increasing recognition of the medical burden has an important public health impact, as the direct costs of bipolar disorder involve not only health costs for the psychiatric component of the disorder but also enormous medical care costs. In the United States alone, the total health care costs for persons with bipolar disorder are estimated to be from 2 to 4 times higher than costs for age- and sex-matched general medical outpatients. A considerable part of these costs (40%) is driven by medical illness.⁵

Altogether, medical and research findings, along with health economic data, support the need to perform a fundamental reexamination of bipolar disorder, leading to a more current view of the disease as a chronic, progressive, multisystem disorder. This new comprehensive framework should guide the search to identify biomarkers and etiologic factors for this disorder. Moreover, it should help design a new policy for health care, including prevention, diagnosis, treatment, and training. In this review, we will report evidence that supports this contemporary and comprehensive vision of bipolar disorder.

METHOD

We conducted a systematic PubMed search of all English-language articles, published between 2000 and 2010, focusing on the English and French literature with *bipolar disorder* cross-referenced with the following search terms: *emotional dysregulation, sleep and circadian rhythm disturbances, cognitive impairment, age at onset, comorbid medical and psychiatric conditions, psychological and medical interventions, outcome, remission,* and *personalized medicine.* The search was conducted between July 2009 and July 2010.

Objectives

The Diagnostic and Statistical Manual of Mental Disorders, Third Revised (DSM-III-R)⁶ and Fourth (DSM-IV) Editions, focus only on circumscribed mood episodes and do not assess the various symptom domains that might be dysfunctional between episodes, including emotional dysregulation, sleep and circadian rhythm disturbances, cognitive impairment, and increased risk for psychiatric comorbidity and medical conditions, which should all be considered as core dimensions of the disorder. Indeed, recent evidence shows that patients with bipolar disorder are symptomatic for almost 50% of their lives, with the majority of patients experiencing subsyndromal depressive symptoms during remitted periods.7 Residual depressive symptoms are associated with an increased risk of relapse, and they contribute to functional impairment.^{8,9} Working along the same lines, the team responsible for the DSM-5 revision process has acknowledged the fact that current criteria need to make prominent use of dimensional measures not only to offer a more accurate phenotypic characterization but also to be able to address the longitudinal and developmental stages of the disorder, to take into account age, sex, and cultural characteristics of each patient, and to test the suitability of biomarkers to serve as risk factors and diagnostic or prognostic tools.¹⁰ We review here the literature (41 articles) to document each of these fields, in between episodes, in order to offer a refined and exhaustive vision of bipolar disorder.

Synthesis: From an Episodic Disorder to a Chronic and Progressive Disorder? Abnormal Emotional Reactivity

It has been observed that patients in a euthymic state of bipolar disorder feel emotions with a higher intensity than nonpsychiatric control subjects. Patients report higher emotional responses and lower thresholds to induced emotional responses when facing minor events.¹¹ Functional brain imaging studies confirm that patients in a euthymic state of bipolar disorder have an increased sensitivity to emotional cues, an inability to regulate mood, and an inability to differentiate between relevant and irrelevant emotional stimuli.¹² Abnormalities in white matter connectivities implicated in emotion regulation have also been observed in bipolar disorder.¹³ Emotional hyperreactivity can be viewed not only as a risk factor for relapses but also as a trait marker for bipolar disorder, as has been evidenced among unaffected relatives.¹⁴ Persistent dysfunction within neural systems underlying emotion regulation has also been found in unaffected firstdegree relatives, suggesting endophenotypes.¹⁵

From a longitudinal perspective, one might hypothesize that interaction between abnormal emotional regulation with genetic and/or environmental vulnerability factors associated with bipolar disorder can exacerbate emotional reactivity, thus inducing mood episodes. For example, patients with bipolar disorder are known to experience hyperreactivity to minor as well as major life events,¹⁶ which might in turn exacerbate emotional reactivity, leading to full-blown episodes. This association might even be strengthened by the fact that individuals with bipolar disorder report more frequent and more severe forms of childhood trauma.¹⁷ In addition, facial emotion recognition, known to impair socioemotional functioning, is consistently abnormal in bipolar disorder.¹⁸ Exaggerated activation in medial prefrontal cortical and subcortical (amygdala and putamen) response to facial expressions of fear and happiness has recently been reported both in euthymic bipolar patients and in unaffected first-degree relatives.¹⁹ Amygdala dysfunction in bipolar disorder is the most commonly and specifically reported finding in functional magnetic resonance imaging (fMRI), with hyperactivity being reported in a variety of paradigms involving facial emotions.²⁰ Abnormal facial recognition might underline disrupted psychosocial and interpersonal functioning which persists between illness episode and may negatively affect quality of life.²¹

Thus, abnormal socioemotional regulation should be viewed as an integral part of bipolar disorder, be systematically assessed, and be the target of specific therapeutic strategies, yet to be developed, in order to delay or prevent episode relapses.

Sleep and Circadian Rhythm Abnormalities

Sleep disturbances (insomnia or hypersomnia) are among the most prominent correlates of mood episodes, and both sleep and circadian disturbances can induce mood episodes.²² Again, significant sleep disturbances characterize periods between episodes. Insomnia, fragmentation of sleep/ wake rhythm, night-to-night sleep variability, longer sleeponset latency, and higher rapid eye movement density have all been reported in patients in a euthymic state of bipolar disorder,²² while actigraphic assessments revealed circadian instability characterized by variability of sleep duration,²³ longer sleep periods, and reduced daytime activity, suggesting a weaker coupling of the circadian system to the external environment.²⁴ Low levels and delayed peak times of melatonin, known to modulate the sleep/wake cycle, have been found in euthymic bipolar patients.²⁵ Several genes known to be important for the generation and regulation of circadian and sleep systems, including TIMELESS, CLOCK, and ARNTL, have been reported to be associated with bipolar disorder.²⁶ Recently, a mouse with a mutation on the Clock gene has been described as a mouse model of mania, with a prolonged circadian period, little need for sleep, and preference for novel stimuli and substance seeking, while these behaviors are reversed with lithium treatment.²⁷

In addition to being among the most frequently reported prodromes of mood episodes, sleep disturbances are known to have detrimental effects on bipolar disorder: pervasive sleep disturbances adversely influence affect regulation both in healthy subjects and in individuals with bipolar disorder. In healthy subjects, sleep loss intensifies negative emotions and increases amygdala response underlying emotional hyperreactivity.²⁸ As suggested by Harvey,²⁴ there might thus be a bidirectional relationship between daytime affect regulation and nighttime sleep. Disturbances in affect regulation during the daytime interfere with sleep and circadian functioning, contributing to emotional dysregulation, thus creating a vicious circle. Thus, sleep disruption and circadian rhythm disturbance abnormalities should both be systematically assessed during the course of the illness and treated to prevent future relapses. Stimuli that can act on the clock, such as bright light exposure, melatonin, manipulation of the sleep/wake rhythm, and interpersonal and social rhythm therapy, have proven efficacy in maintenance treatment.²⁹

Cognitive Impairment

There is a broad consensus that patients with bipolar disorder have cognitive impairments in attention, memory, and executive function.³⁰ Some of these impairments appear early in the course of bipolar disorder and persist over time in euthymic patients, while minor working memory dysfunction has been reported in unaffected relatives of individuals with bipolar disorder, thus suggesting that cognitive impairments may represent a trait marker of bipolar disorder.³¹ Evidence for accelerated cognitive decline in bipolar disorder is only preliminary, but verbal learning and memory deficits are thought to be the consequence of the progression of the disorder.³²

Cognitive impairments need to be precisely and regularly assessed during follow-up in order to plan personalized cognitive remediation. Indeed, the relationship between cognitive impairment and functioning appears to be even stronger than that between subsyndromal symptoms and psychosocial functioning. Delayed verbal recovery of information is the cognitive measure that best predicts poor functional outcome.³² Poor adherence to treatment, observed in more than 60% of individuals with bipolar disorder,³³ is a substantial problem, and it appears to be closely associated with persistent cognitive dysfunction during remission.³⁴

Thus, each of these 3 symptomatic dimensions are dysfunctional to some extent between mood episodes, each can be precisely measured by clinical assessment or objective measurement, each may be considered a persistent marker of the disorder, and each may, alone or in combination with other dimensions cited here, induce a mood episode. To better treat individuals with bipolar disorder and prevent relapses, emotional dysregulation, sleep/circadian disturbances, and cognitive functions need to be regularly assessed along the life cycle in order to plan specific and personalized treatments. Such markers already exist but are not yet routinely examined. For example, self-rating questionnaires of emotional reactivity such as the Affective Lability Scale, the Affect Intensity Measure, or the Multidimensional Assessment of Thymic States scale,³⁵ and arousal induction paradigms would help monitor the effectiveness of a specific cognitive therapy. Actigraphy, along with circadian and sleep questionnaires, should help in the identification of individuals with bipolar disorder who could benefit from interventions targeting social and sleep/wake rhythms. Trauma questionnaires could enable the identification of individuals who might benefit from trauma-focused interventions, while skin conductance assessment could identify individuals who might respond to cognitive therapy aimed at reducing stress response. Systematic assessment of cognitive functioning would enable the design of cognitive remediation programs that could improve functional outcome.

While most recent treatment guidelines³⁶ include pharmacotherapy as well as psychosocial interventions as maintenance treatment for bipolar disorder, the majority of treatment recommendations are still focused on alleviation of acute symptoms, and they remain based on limited objective data, ignoring the heterogeneity of bipolar disorder, which probably makes patients more or less likely to respond to specific treatments, thus leaving considerable areas of uncertainty. We thus propose here the basis for building a combination of psychosocial interventions³⁷ tailored to the needs of each patient, assessed while euthymic, and provided at any given point during the trajectory of the disorder. Complementary to pharmacotherapy and nonspecific psychotherapy, the therapeutic ingredients of these personalized strategies could be composed of, for example, communication/social training, problem solving regarding stressful events, sleep/wake cycle regulation, and cognitive remediation. In addition, as burdens experienced by family caregivers of individuals with bipolar disorder are associated with problems in health, mental health, and cost, psychosocial interventions in caregivers are needed.³⁸ In the future, the impact of such "intervention packages" would have to be measured with objective assessments of specific dimensions to be improved, as well as functional outcome measured, for example, by daily functioning or by adherence to treatment and by general issues such as cost effectiveness, with the ultimate goal of reducing resource utilization in the medium to long term.

Another unexplored territory is the applicability of personalized psychosocial approaches to early-onset bipolar disorder and to children and adolescents at risk for bipolar disorder. This issue is of utmost importance, as patients with an early onset of bipolar disorder are known to have a poor prognosis in comparison to patients with intermediate and late onset.^{39,40} Early intervention may also lessen the morbidity and improve the course and outcome of bipolar disorder for children. Targeting specific difficulties of youth, such as working on stabilization of sleep/wake cycles, reducing family conflict, and explaining the risks associated with drug abuse, could help minimize the severity of early-onset bipolar disorder.⁴¹ In addition to age issues, future research needs to identify specific factors that might be related to course and outcome in minority populations, as this information might help to identify the components of interventions that have to be modified when working with different populations (eg, different sex, socioeconomic, cultural, and ethnic groups).

From a Mental Disorder to a Multisystem Disorder

Aside from the bipolar diagnosis itself and its consequences, such as disability and unemployment, a large array of comorbid psychiatric conditions is associated with bipolar disorder. Up to 75% of patients with bipolar disorder have at least 1 other psychiatric disorder, with anxiety, substance abuse, and eating disorder among the most common.^{42,43} In the past, excess deaths associated with bipolar disorder were attributed to unnatural causes such as suicide, homicide, and accidents. Increased evidence now reveals that patients with bipolar disorder are, in fact, mainly at risk of premature death because of medical disorders, with excess mortality ranging from 35% to 2-fold higher than the general population and higher than those with major depression.⁴⁴ The most common causes of natural death for bipolar patients are cardiovascular and cerebrovascular diseases, which occur at twice the rate of that in the general population.⁴⁴ Bipolar patients are at greater risk for cardiovascular mortality than patients with other mental illnesses, including unipolar depression and schizophrenia. Bipolar patients have a higher prevalence of medical disorders that are themselves cardiovascular risk factors, such as diabetes mellitus underlined by impaired glucose tolerance and insulin resistance, obesity (and in particular increased rates of abdominal obesity), hypertension associated with higher sympathetic tone and lower heart rate variability, and thyroid failure.⁴⁵ Obesity is correlated with a poorer outcome in patients with bipolar I disorder. Preventing and treating obesity in bipolar disorder patients could thus decrease the morbidity and mortality related to physical illness and possibly improve the course of bipolar illness.46

Identification of these risk factors should be performed early in the course of bipolar disorder, as it is noteworthy that the increase in mortality is most prominent in the first 10 years after admission for a mood episode. In children and adolescents with pediatric bipolar disorder, comorbid medical conditions, such as obesity, type 2 diabetes, and cardiovascular disorders were more prevalent than in a random sample of 4,500 children not treated for psychiatric disorders, and these comorbid medical conditions preceded the diagnosis of bipolar disorder.⁴⁷

Excess mortality from natural causes among bipolar patients may result from several mechanisms. Bipolar disorder is associated with an excess burden of cardiovascular risk factors, such as smoking (70% of outpatients with bipolar disorder are nicotine dependent), alcoholism, poor diet, and sedentary lifestyle.⁴⁸ In the Systematic Treatment Enhancement Program for Bipolar Disorder study, substance abuse and smoking were found to be associated with more lifetime mood episodes and greater severity of symptoms, as well as with rapid cycling, comorbid psychiatric disorders, and demographic factors such as being male, having less education, and having lower income.⁴³ In addition, nearly all antipsychotic medications and mood stabilizers cause some amount of weight gain, from minimal to significant amounts. The role of these medications in the metabolic syndrome may be substantial, as is their benefit in the treatment of psychiatric illness. Until more is known about the source of increased risk of cardiovascular disorder and of other risks, such as diabetes, it is the responsibility of the physician to provide careful monitoring of these risk factors, for example, by providing help for smoking cessation or reinforcing the need to do structured exercise⁴⁹ and to make a careful selection of treatments, antipsychotic medications, and/or mood stabilizers, according to the expected risk-benefit ratio for a given patient.

In addition to an unhealthy lifestyle, which may contribute to the risk of medical disorders, elucidating the mechanisms underlying the links between specific medical illness and bipolar disorder may provide new insights into its pathophysiology. Alterations in interacting metabolic, inflammatory, and oxidative systems appear likely to contribute to the cumulative "organ damage," eg, allostatic load.⁵⁰ For example, major stressors have been reported during the childhood of bipolar patients,¹⁷ and they often precede mood episodes. Abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis, central to stress response, have been reported during mood episodes, during euthymic periods, and in unaffected relatives of patients with bipolar disorder, thus suggesting that HPA axis dysfunction may be a vulnerability marker.⁵¹ HPA axis dysfunction may in turn increase insulin resistance, leading to hyperglycemia, increased oxidative stress, metabolic syndrome, and atherosclerosis. Hyperactivity of the HPA axis may also be associated with hyperactivity of the autonomous system, commonly observed in patients with bipolar disorder and their relatives.¹⁴ Dysregulation of the autonomic system may lead to insulin resistance and may worsen metabolic syndrome, leading to increased risk of sudden cardiac death.48

Recently, attention has shifted to the importance of inflammation in the pathophysiology and treatment of bipolar disorder. Indeed, several studies have shown that bipolar disorder is associated with increased expression of proinflammatory markers (particularly C-reactive protein, soluble interleukin-2 receptor, interleukin-6 [IL-6], and tumor necrosis factor): genetic findings suggest that bipolar disorder is associated with interleukin-1 and IL-6 genes, and comorbid medical burden may contribute to the proinflammatory milieu. Lithium may modulate the inflammation milieu in bipolar disorder, and anti-inflammatory therapies may possess symptom-alleviating effects among acutely ill patients.⁵¹ For example, bipolar patients have elevated levels of IL-6, a potent stimulator of corticotrophin-releasing hormone production that may also lead to HPA axis hyperactivity and hypercortisolemia, acting synergistically to worsen cardiovascular outcome. In turn, elevation of cortisol can increase levels of proinflammatory cytokines and downregulate cellular and humoral responses. Inflammation has also been hypothesized to signal the brain to produce neurobiological changes in the face of stress.⁵² There is an urgent

need for further research to understand the putative role of inflammation in bipolar disorder.

A clear role for basic research is required in the previously described areas. First, identification of core markers of the disorder would help phenotypic refinement, and it might improve the impact of basic neuroscience tools, such as brain imaging techniques or molecular biology, on elucidating the pathophysiology of bipolar disorder. Second, bipolar disorder is increasingly recognized as being a multisystem disorder that affects endocrine, vascular, immunologic, and neural functions. Elucidating the links between specific medical illnesses and bipolar disorder may provide new approaches to better understand and treat the disorder. In addition, this approach should stimulate the identification of biomarkers or biosignatures of the disorder that would enable us to better identify diagnostic risk and protective factors at the individual level (as opposed to the population level) and to develop a new set of personalized interventions. These factors would span genetic, neurobiologic, behavioral, and environmental markers along with age, sex, ethnicity, culture, and socioeconomic background, either alone or in combination, in order to build personalized approaches to treatment.

DISCUSSION

Toward a New, Integrated Medical Care System for Individuals With Bipolar Disorder

Despite the recognition that the long-term outcome of bipolar disorder depends on systematic assessment of both interepisodic dysfunctional domains and comorbid psychiatric and medical conditions, treatment of bipolar disorder still focuses mostly on alleviation of acute symptoms and prevention of future recurrences. In addition, current guidelines advocate more or less similar treatment algorithms for all patients, ignoring the clinical, pathophysiological, and lifetime heterogeneity of bipolar disorder that makes certain patients more or less likely to respond to specific treatment. Even when diagnosis is established, the management of bipolar disorder remains a major challenge, as only suboptimal treatments are offered to patients in both Europe and the United States.⁵³ Thus, we need to develop personalized health care, and treatment targets should move beyond acute symptoms and prevention of mood episodes to address cognitive deficits, emotional dysregulation, sleep and circadian problems, and reduction of medical risk factors. Health care factors, such as lack of clinician training to address these questions, lack of comprehensive assessment, and lack of systematic follow-up, need to be rapidly changed in developed countries to diminish the burden and costs associated with bipolar disorder.

Reorganization of medical health care to face these basic needs is of great importance given the enormous consequences of bipolar disorder in terms of suffering for the patients and their relatives and public health costs.⁴² Total bipolar disorder management and treatment costs in the United States were estimated in 2003 at \$30.4 to \$43.7 billion.

The lifetime direct cost of bipolar disorder was estimated at \$13 billion in 1998, and the cost of managing a single patient was estimated at more than \$3,400 per year in 1999. These data are probably underestimated, as indirect costs, presumed to be significant, are missing. In the United Kingdom, the estimated cost is £4.59 billion (2007 value), well above the economic burden of diabetes, which is close to £3.5 billion per year. The yearly United Kingdom estimate for indirect costs was £1,510 million for unemployment, while the estimate for The Netherlands was £1,370 million.⁴²

These data clearly identify bipolar disorder as a major mental health issue and an area of unmet clinical and research needs. The burden of the disease to patients is considerable, and to date it has been underrecognized. New integrated care systems must be developed, including the following aspects:

(1) Multidisciplinary, systematic, and comprehensive assessment of all facets of bipolar disorder allowing early diagnosis based on a lifetime description of bipolar disorder. Assessment should include not only dimensional assessments and cognitive evaluation to identify subtle impairments but also comorbid psychiatric disorders and medical risk factors. These evaluations should be performed by a multidisciplinary team specialized in the field of bipolar disorder and integrating physicians, psychiatrists, and psychologists.

(2) A personalized mental health treatment program prescribed according to the medical workup performed and including, for example, the selection of mood stabilizers on the basis of risk-benefit assessment, a combination of primary prevention strategies, such as psychoeducation, increased physical activity, diet improvement, and secondary interventions with targeted treatments, such as cognitive therapy, interpersonal social rhythm therapy, cognitive remediation, and/or stress alleviation techniques.

(3) Regular follow-up monitoring of risk factors, evaluating the impact of treatments on improving outcomes, assessing risk factors, and monitoring the evolution of a chronic disorder along the life cycle.

An example of such a strategy is presently developed in France within the FondaMental Foundation, created in 2007 by the French Ministry of Research and within the network European Network of Bipolar Expert Centers appointed in 2008 by the European Commission. Expert centers are based on a multidisciplinary approach performed by a network of highly specialized medical teams. A common set of clinical procedures, on the basis of exhaustive and multidimensional assessments, has been selected in order to provide accurate therapeutic advice. Expert centers use the same Web application, "e-bipolar," developed to perform patient follow-up as well as research. Data are collected in expert centers and then aggregated into an anonymous national database, thus simultaneously improving health care, translational research, patient education, and training of practitioners.⁵⁴ This initiative introduces a new model for clinical collaborations between expert centers and local clinicians (general practitioners and psychiatrists) on one hand, and between expert centers and researchers for improving knowledge of bipolar disorder on the other hand. The long-term goal, in keeping with the ideas of Insel,⁵⁵ is to better integrate academic and clinical practice in order to reduce the gap between research, training, and effective health care, thus paving the way for prevention, recovery, and the cure of bipolar disorder.

CONCLUSION

High rates of misdiagnosis, delayed diagnosis, and lack of recognition and treatment of comorbid conditions often lead patients with bipolar disorder to have a chronic course of illness, with high disability, unemployment rates, and mortality. Inattention to and underrecognition of comorbid medical illnesses are the source of huge suffering, costs, and premature deaths.⁴⁵ Key problems include discrimination against the mentally ill, little integration of somatic and psychiatric health care, a paucity of funding of general somatic care, and lack of information given to the patients, leading them to view their psychiatric care as their most important form of medical care. Disparity and inadequate care raise key questions for those in the medical community, health policy makers, individuals with bipolar disorder, and caregivers, and they pose important research challenges.

The organization of mental health and medical care services should better serve the needs of patients. Training initiatives should increase general medical education in psychiatric training and psychiatric education in medical training. Patients, caregivers, and the general public should receive systematic information on relevant psychiatric and medical issues. Providing optimal assessment, prevention, and treatment to this highly vulnerable population requires urgent action.

Drug names: Lithium (Lithobid and others).

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