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ABSTRACT

Objectives

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 inter-episodic dysfunctional domains and comorbid psychiatric and medical conditions, treatment of bipolar disorder still mostly focuses primarily on alleviation of acute symptoms and prevention of future recurrences. We propose here to review the evidence offering a current view of bipolar disorder defined as a chronic and progressive multi-system 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: emotions, sleep, cognition, onset, comorbidities, psychosocial and medical interventions, outcome, and personalized medicine.

Study Selection

Forty-one papers 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 Extraction

Since this is a review of the literature and not a meta-analysis, no data extraction occurred.

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 inter-episodic dimensions along with comorbid medical and psychiatric risk factors should be performed along the life cycle in order to plan specific and personalized pharmacological, 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 current view of bipolar disorder as a chronic, progressive, multi-system disorder. This new comprehensive framework should guide the search to identify biomarkers and etiological factors and should help design a new policy for health care including prevention, diagnosis, treatment, and training.

According to the World Health Organization (WHO), bipolar disorder is the sixth cause of disability-adjusted life years among all other diseases.[1] In addition to traditional bipolar I subtype defined by episodes of mania and depression, 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 in between mood episodes. This revised view should not only challenge 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 inter-episodic dimensions and risk factors in order to obtain better long-term prognoses. Greater awareness of medical burden associated with bipolar disorder calls for an integrated medical care model. Increasing the recognition of medical burden has important public health impact as the direct cost of bipolar disorder not only involves health costs for the psychiatric component of the disorder, but also enormous medical care costs. In the US alone, the total health cost for persons with bipolar disorder is estimated to be between two to four 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, multi-system disorder. This new comprehensive framework should guide the search to identify biomarkers and etiological 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.

Methods

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: emotions, circadian rhythm, cognition, age at onset, comorbid medical conditions, psychological and medical interventions, outcome, remission, and personalized medicine.

Objectives

The third (DSM-III) and fourth (DSM-IV) edition of DSM[6] only focus on circumscribed mood episodes and do not assess the various symptom domains which might be dysfunctional between episodes, including emotional dysregulation, sleep and circadian rhythm disturbances, cognitive impairment, 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 almost 50% of their lives, with the majority of patients experiencing sub-syndromal depressive symptoms during remitted periods.[7] Residual depressive symptoms are associated with an increased risk of relapse and contribute to functional impairment.[8,9] Working along the same lines, the DSM-V revision process has

acknowledged the fact that current criteria need not only to make prominent use of dimensional measures 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, gender, and cultural characteristics of each patient, and to test the readiness of biomarkers to serve as risk factors and diagnostic or prognostic tools.[10] We review here the literature 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 non-psychiatric control subjects. Patients report higher emotional responses and lower thresholds to induced emotional responses 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 hyper-reactivity 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 first-degree 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 hyper-reactivity to minor as well as major life events,[16] which might in turn enhance emotional reactivity leading to full blown episodes. This 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 socio-emotional 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 socio-emotional 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] Here again, significant sleep disturbances characterize periods in between episodes. Insomnia, fragmentation of sleep/wake rhythm, night-to-night sleep variability, longer sleep onset latency, and higher REM 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 generation and regulation of circadian and sleep systems have been reported to be associated with bipolar disorder including Timeless, Clock, and Bmal1.[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 one of the most frequently reported prodromes of mood episodes, sleep disturbances are known to have detrimental effects on bipolar disorder: pervasive sleep disturbances are critical for affect regulation both in normal subjects and in individuals with bipolar disorder. In normal subjects, sleep loss intensifies negative emotions and increases amygdala response underlying emotional hyper-reactivity.[28] As suggested by Harvey,[24] there might thus be a bidirectional relationship between daytime affect regulation and night time 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 on 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 they 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 of cognitive impairment and functioning appear to be even stronger than between sub-syndromal 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 appears to be closely associated to persistent cognitive dysfunction during remission.[34]

Thus, each of these three symptomatic dimensions are dysfunctional to some extent in between the mood episodes, each can be precisely measured by clinical assessment or objective measurement, each may be considered as a persistent marker of the disorder, and 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 (ALS), Affect Intensity Measure (AIM), or Multidimensional Assessment

of Thymic States (MATHYS) 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 guidelines[36] 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 remain based on limited objective data, ignoring the heterogeneity of BP 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 interventions[37] tailored to the needs of each patient, assessed while euthymic, and provided at any given point during the trajectory of their disorder. Complementary to pharmacotherapy and non-specific 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 on general issues such as cost effectiveness with the ultimate goal to reduce 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 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 risk 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 might help to identify the components of interventions that have to be modified when working with different populations (e.g., different gender, socio-economic, cultural, and ethnic groups).

<u>From a mental disorder to a multisystem disorder</u>

Aside from the bipolar diagnosis itself and its consequences such as disability and unemployment, there is a large array of comorbid psychiatric conditions associated with bipolar disorder. Up to 75% of patients with bipolar disorder have at least one 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 twofold 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 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 which 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 pediatric bipolar disorder, comorbid medical conditions such as obesity, type 2 diabetes, and cardiovascular disorders were more prevalent and 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 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 STEP-BD program, substance abuse and smoking were found to be associated with more lifetime mood episodes and greater severity of symptoms, as well as rapid cycling, comorbid psychiatric disorders, and demographic factors such as being male, having less education, and having lower income.[43] In addition, nearly all

antipsychotics and mood stabilizers cause some amount of weight gain from minimal to significant amounts. Their role 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 exercise[49] and to make a careful selection of treatments, antipsychotics, 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," e.g., allostatic load.[50] For example, major stressors have been reported during the childhood of bipolar patients[17] and 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 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 pro-inflammatory markers (particularly CRP, soluble IL-2 receptor, IL-6, and TNF): genetic findings suggest that bipolar disorder is associated with IL-1 and IL-6 genes, and comorbid medical burden may contribute to the pro-inflammatory 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 interleukin-6, a potent stimulator of corticotrophin-releasing hormone production which 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 down-regulate 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 might improve the impact of basic neuroscience tools such as brain imaging techniques or molecular biology to elucidate pathophysiology of bipolar disorder. Second, bipolar disorder is increasingly recognized as being a multi-system 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 to better 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 population level) and to develop a new set of personalized interventions. These

factors would span genetic, neurobiological, behavioral, and environmental markers along with age, gender, ethnicity, culture, and socioeconomic background, either alone or in combination, in order to build personalized approaches to treatment.

Discussion: Towards a new integrated medical care system for individuals with bipolar disorder

Despite the recognition that long term outcome of bipolar disorder depends on systematic assessment of both inter-episodic dysfunctional domains and comorbid psychiatric and medical conditions, treatment of bipolar disorder still mostly focuses 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 which 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 both in 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 that of cognitive deficits, emotional dysregulation, sleep and circadian problems, as well as 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 in terms of public health cost.[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 $3400 per year in 1999. These data are probably under-estimated as indirect costs, presumed to be significant, are missing. In the UK, 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 UK estimate for indirect costs was £1510 million for unemployment, while the Dutch estimate was £1370 million.

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 has been under-recognized. 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 psychiatric comorbid 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 work-up performed and including, for example, a selection of a mood-stabilizers based on risk-benefit assessment, a combination of primary prevention strategies such as psycho-education, increased physical activity, diet improvement, and secondary interventions with targeted treatments such as cognitive therapy, interpersonal social rhythm therapy (IPSRT), cognitive remediation, and/or stress alleviation techniques.

(3) Regular follow-up monitoring of risk factors, evaluating the impact of treatments to improve outcome, 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 ENBREC (European Network of Bipolar Expert Centers) appointed in 2008 by the European Commission. Expert centers are based on a multi-disciplinary approach performed by a network of highly specialized medical teams. A common set of clinical procedures based on exhaustive and multidimensional assessments have 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 to improve knowledge on 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 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 illness to have a chronic course with high disability, unemployment rates, and mortality. Inattention and under-recognition of comorbid

medical illnesses are the source of huge suffering, costs, and premature deaths.[45] Key problems include discrimination of the mentally ill, little integration of somatic and psychiatric health care, 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 raises key questions for those in the medical community, health policy makers, individuals with bipolar disorder, and caregivers and 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 increase 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.

References

1. Murray C, Lopez A. The global burden of disease. A comprehensive assessment of morbidity and disability from diseases, injuries and risk factors in 1990 and projected to 2020. *Harvard University Press.* Cambridge, Massachusetts:1996.

2. Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, Petukhova M, Kessler RC. Lifetime and 12-months prevalence of bipolar spectrum disorder in the national comorbidity survey replication. *Arch Gen Psychiatry.* 2007;64:543-552.

3. Hirschfeld RM, Calabrese JR, Weissman MM, Reed M, Davies MA, Frye MA, et al. Screening for bipolar disorder in the community. *J Clin Psychiatry.* 2003;64(1):53-59.

4. Baca-Garcia E, Perez-Rodriguez MM, Basurte-Villamor I, Lopez-Castroman J, Fernandez del Moral AL, Jimenez-Arriero MA, et al. Diagnostic stability and evolution of bipolar disorder in clinical practice: a prospective cohort study. *Acta Psychiatr Scand.* 2007;115(6):473-480.

5. Bryant-Comstock L, Stender M, Devercelli G. Health care utilization and costs among privately insured patients with bipolar I disorder. *Bipolar Disord.* 2002;4:398-405.

6. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 3rd ed, revised. *American Psychiatric Association.* Washington, DC, 1987.

7. Judd LL, Akiskal H, Schettler PJ, Endicott J, Maser J, Solomon DA, Leon AC, Rice J, Keller MB. Long term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry.* 2002;59:530-537.

8. Fagiolini A, Kupfer DJ, Masalehdan A, Scott JA, Houck PR, Frank E. Functional impairment in the remission phase of bipolar disorder. *Bipolar Disord.* 2005;7(3):281-285.

9. Altshuler LL, Post RM, Black DO et al. Subsyndromal depressive symptoms are associated with functional impairment in patients with bipolar disorder: results of a large multsite study. *J Clin Psychiatry.* 2006;67:1551-1560.

10. Regier DA, Narrow WE, Kuhl EA, Kupfer DJ. The conceptual development of DSM-V. *Am J Psychiatry*. 2009 Jun;166(6):645-50.

11. Henry C, Van den Bulke D, Bellivier F, Roy I, Swendsen J, M'Baïlara K, Siever LJ, Leboyer M. Affective labiality and affect intensity as core dimensions of bipolar disorders during euthymic periods. *Psychiatry Res.* 2008;159(1-2):1-6.

12. Phillips ML, Ladouceur CD, Drevets WC. A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. *Mol Psychiatry.* 2008;13(9):829,833-835.

13. Houenou J, Wessa M, Douaud G, Leboyer M, Chanraud S, Perrin M, Poupon C, Martinot JL, Paillere-Martinot ML. Increased white matter connectivity in euthymic bipolar patients: diffusion tensor tractography between the subgenual cingulate and the amygdalo-hippocampal complex. *Mol Psychiatry.* 2007;12(11):1001-1010.

14. Zahn TP, Nurnberger JI Jr, Berrettini WH. Electrodermal activity in young adults at genetic risk for affective disorder. *Arch Gen Psychiatry.* 1989;46(12):1120-1124.

15. Kruger S, Alda M, Young LT, Goldapple K, Parish S, Mayberg HS. Risk and resilience markers in bipolar disorder: brain response to emotional challenge in bipolar patients and their healthy siblings. *Am J Psychiatry.* 2006;163:257-264.

16. Malkoff-Schwartz S, Frank E, Anderson B et al. Stressful life events and social rhythm disruption in the onset of bipolar and unipolar episodes. *Arch Gen Psychiatry*. 1998;55:702-707.

17. Etain B, Henry C, Bellivier F, Mathieu F, Leboyer M. Beyond genetics: childhood affective trauma in bipolar disorder. *Bipolar Disord.* 2008;10(8):867-876.

18. McClure-Tone E. Socioemotional functioning in bipolar disorder versus typical development: behavioral and neural differences. *Clin Psychol Sci Pract*. 2009;16:98-113.

19. Surguladze SA, Larshall N, Schulze K, Hall MH, Walshe M, Bramon E, Phillips M, Murray R, McDonald C. Exaggerated neural response to emotional faces in patients with bipolar disorder and their first degree relatives. *NeuroImage.* 2010;Epub ahead of print.

20. Almeida J, Versace A, Hassel S, Kupfer D, Phillips M. Elevated amygdala activity to sad facial expressions: a state marker of bipolar but not unipolar depression. *Biol Psychiatry.* 2010;67:414-421.

21. Rosa AR, Reinares M, Franco C, Comes M, Torrent C, Sanchez-Moreno J, Martinez-Aran A, Salamero M, Kapczinski F, Vieta E. Clinical predictors of functional outcome of bipolar patients in remission. *Bipolar Disorder.* 2009;11:401-409.

22. Harvey A. Sleep and circadian rhythms in bipolar disorder: seeking synchrony, harmony, and regulation. *Am J Psychiatry.* 2008;165(7):820-829.

23. Millar A, Espie CA, Scott J. The sleep of remitted bipolar outpatients: a controlled naturalistic study using actigraphy. *J Affect Disord.* 2004 Jun;80(2-3):145-53.

24. Harvey A, Schmidt D, Scarna A, Semler C, Goodwin G. Self related functioning in euthymic patients with bipolar disorder, patients with insomnia and subjects without sleep problems. *Am J Psy*. 2005;162(1):50-59.

25. Nurnberger JI, Adkins S, Lahiri DK, Mayeda A, Hu K, Lewy A, Miller A, Bowman ES, Miller MJ, Rau L, Smiley C, Davis-Singh D. Melatonin suppression by light in euthymic bipolar and unipolar patients. *Arch Gen Psychiatry.* 2000;57:572–579.

26. Mansour HA, Monk TH, Nimgaonkar VL. Circadian genes and bipolar disorder. *Ann Med.* 2005;37:196–205.

27. Roybal K, Theobold D, Graham A, DiNieri JA, Russo SJ, Krishnan V, Chakravarty S, Peevey J, Oehrlein N, Birnbaum S, Vitaterna MH, Orsulak P, Takahashi JS, Nestler EJ, Carlezon WA, McClung CA. Mania-like behavior induced by disruption of CLOCK. *Proc Natl Acad Sci U S A.* 2007;10:104(15):6097-98.

28. Yoo S-S, Gular N, Hu P, Jolesz FA, Walker MP. The human emotional brain without sleep - a prefrontal amygdala disconnect. *Curr Biol.* 2008;17(20):R877-878.

29. Frank E, Kupfer DJ, Thase ME, Mallinger AG, Swartz HA, Eagiolini AM, Grochocinski V, Houck P, Scott J, Thompson W, Monk T. Two-year outcomes for interpersonal and social rhythm therapy in individuals with bipolar I disorder. *Arch Gen Psychiatry.* 2005; 62:996–1004.

30. Goodwin G, Martinez-Aran A, Glahn D, Vieta E. Cognitive impairment in bipolar disorder: Neurodevelopment or neurodegeneration? An ECNP expert meeting report. *Eur Neuropsychopharmacol.* 2008;18:787-793.

31. Arts B, Jabben N, Krabbendam L, Van Os J. Meta-analyses of cognitive functioning in euthymic bipolar patients and their first degree relatives. *Psychol Medicine.* 2008;38(6):771-785.

32. Martinez-Aran A, Vieta E, Torrent C, Sanchez-Moreno J, Goikolea JM, Salamero M,Malhi GS, Gonzales-Pinto A, Daban C, Varez-Grandi S, Fountoulakis K, Kaprinis G, Tabares-Seisdedos R, Ayusi-Mateos JL. Functional outcome in bipolar disorder: the role of clinical and cognitive factors. *Bipolar Disord.* 2007;9:103-113.

33. Colom F, Vieta E, Martínez-Arán A, Reinares M, Benabarre A, Gastó C. Clinical factors associated with treatment noncompliance in euthymic bipolar patients. *J Clin Psychiatry*. 2000 Aug;61(8):549-5.

34. Martinez-Aran A, Scott J, Colom F, Torrent C, Tabares-Seisdedos R, Daban C, Leboyer M, Henry C, Goodwin GM, Gonzalez-Pinto A, Cruz N, Sanchez-Moreno J, Vieta E. Treatment nonadherence and neurocognitive impairment in bipolar disorder. *J Clin Psychiatry*. 2009 Jul;70(7):1017-2.

35. Henry C, M'Bailara K, Lépine J.P., Lajnef M, Leboyer M. Defining bipolar mood states with quantitative measurements of inhibition/activation and emotional reactivity. *J Affect Disord.* 2010;Epub ahead of print.

36. Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Möller HJ, Kasper S. WFSBP Task Force On Treatment Guidelines For Bipolar Disorders. The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Update 2010 on the treatment of acute bipolar depression. *World J Biol Psychiatry*. 2010 Mar;11(2):81-10.

37. Vieta E, Pacchiarotti I, Valenti M, Berk M, Scott J, Colom F. A critical update on psychological interventions for bipolar disorders. *Curr Psychiatry Reps.* 2009;11:494-502.

38. Perlick DA, Rosenheck RR, Miklowitz DJ, Chessick C, Wolff N, Kaczynski R, et al. Prevalence and correlates of burden among caregivers of patients with bipolar disorder enrolled in the Systematic Treatment Enhancement Program for Bipolar Disorder. *Bipolar Disorders*. 2007;9:262–273.

39. Schurhoff F, Bellivier F, Jouvent R, Mouren-Simeoni MC, Bouvard M, Allilaire JF, Leboyer M. Early and late onset bipolar disorders: two different forms of manic depressive illness? *J Affect Disord.* 2000;58:215-221.

40. Perlis RH, Dennehy EB, Miklowitz DJ, DelBello MP, Ostacher M, Calabrese JR, Amtrano RM, Wisniewski SR, Bowden CL, Thase ME, Nierenberg AA, Sachs G. Retrospective age at onset of bipolar disorder and outcome during a two-year follow-up: results from the STEP-BD study.

41. Miklowitz DJ, Scott J, Psychosocial treatments for bipolar disorder: cost-effectivness, mediating mechanisms, and future direction. *Bipolar Disorders.* 2009;11(2):110-122.

42. Fajutrao L, Locklear J, Priaulx J, Heyes A. A systematic review of the evidence of the burden of bipolar disorder in Europe. *Clin Prac Epidemiol Ment Health.* 2009;5:3.

43. Parikh S, LeBlanc S, Ovanessian M. Advancing bipolar disorder: Key lessons from the systematic treatment enhancement program for Bipolar disorder (STEP-BD). *Can J Psychiatry.* 2010;55(3):136-142.

44. Roshanaei-Moghaddam B, Katon W. Premature mortality from general medical illnesses among persons with bipolar disorder: a review. *Psychiatr Serv.* 2009;60(2):147-156.

45. Kupfer D. The increasing medical burden in bipolar disorder. *JAMA.* 2005;293(20):2528-2530.

46. Fagiolini A, Kupfer D, Houck PR et al. Obesity as a correlate of outcome in patients with bipolar I disorder. *Am J Psychiatry.* 2003;160(1):112-117.

47. Jerrell J, McIntyre R, Tripathi A. A cohort study of the prevalence of comorbid medical conditions in pediatric bipolar disorder. *J Clin Psychiatry.* 2009.

48. Taylor V, McQueen G. Association between bipolar disorder and metabolic syndrome; a review. *J Clin Psychiatry*. 2006;67:1034-1041.

49. Alsuwaidan M, Kucyi A, Law C, McIntyre R. Exercise and Bipolar disorder: a review of neurobiological mediators. *Neuromol Med*. 2009;11:328-336.

50. McEwen BS. Protection and damage from acute and chronic stress allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. *Ann N Y Acad Sci.* 2004;1032(1):1-è.

51. Goldstein BI, Kemp DE, Soczynska JK, McIntyre RS. Inflammation and the phenomenology, pathophysiology, comorbidity, and treatment of bipolar disorder. *J Clin Psychiatry.* 2009;70(8):1078-1090.

52. Kronfol Z, Remitz DG. Cytokines and the brain: implications for clinical psychiatry. *Am J Psychiatry.* 2000;157:683-694.

53. Scott J, Paykel E, Morriss R, Bentall R, et al. A randomized controlled trial of CBT versus usual treatment in severe and recurrent bipolar disorders. *Br J Psychiatry.* 2006;188:313-320.

54. Henry C, Etain B, Mathieu F, Raust A, Vibert JF, Raust A, Scott J, Leboyer M. FondaMental bipolar expert centres: developing a thematic network to close the gap between research knowledge and effective care and treatment. (Submitted).

55. Insel T. Translating scientific opportunity into public health impact. *Arch Gen Psychiatry.* 2009;66(2):128-133.