SPECIAL ARTICLE

How to prevent the malignant progression of bipolar disorder

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There is increasing recognition that, in a high percentage of cases, bipolar disorder is a progressive illness. Multiple types of sensitization (or increased reactivity to repetition of the same stimulus) drive illness progression. One of the clearest is that of episode sensitization, where increased numbers of prior episodes are associated with: faster recurrences; more dysfunction; disability; social, educational, and employment deficits; suicide; medical comorbidities; cognitive dysfunction; and an increased incidence of dementia in old age. Repetition of stressors and bouts of substance abuse can also result in sensitization. Each type of sensitization appears to have an epigenetic basis, such that preventing sensitization should minimize the accumulation of adverse epigenetic chemical marks on DNA, histones, and microRNA. New data emphasize the importance of early, consistent intervention after an initial manic episode. The cognitive dysfunction associated with a first episode improves only if there are no further episode recurrences during the next year. A randomized study has also shown that comprehensive multimodal prophylactic intervention for 2 years leads to improvements in illness course extending over a total of 6 years. Intensive treatment of the earliest stages of bipolar disorder can thus exert lasting positive effects on the course of illness.

Keywords: Sensitization; kindling; epigenetic; stress; depression

Introduction

Many of the clinical characteristics of bipolar disorder show sensitization (increases in pathological behavioral reactivity to repetition of the same stimuli) rather than tolerance or downregulation (Box 1). This includes sensitization to recurrent stressors, mood episodes, and bouts of substance abuse. Each type of sensitization also shows cross-sensitization to the other two, resulting in a downward spiral of illness progression.[1-3]

While stress, episodes, and bouts of substance abuse sensitize, the unfolding of recurrent mood episodes shows a pattern resembling that of amygdala kindling. In kindling, repeated stimulation of the amygdala results in increasingly long and complex afterdischarges which culminate in unilateral, then bilateral, full-blown seizures in response to a previously subthreshold stimulus. Following enough seizures so triggered, spontaneous seizures also begin to occur. While kindling is a nonhomologous model for affective episodes, the course of mood episodes proceeding from multiple recurrences precipitated by stressors to those that occur more spontaneously is analogous to the progressive unfolding and progression of amygdala-kindled seizures.[4] In this fashion, the sensitization and kindling preclinical models help conceptualize different aspects of biochemical, physiological, and behavioral aspects of illness progression in the affective disorders.

The sensitization phenomena and the kindling-like illness progression of affective episodes also emphasize the importance of early and sustained prophylactic intervention before the illness becomes increasing complex and treatment-resistant, a phenomenon that occurs both in the clinical realm and in the animal models. Moreover, since minor behavioral abnormalities and partial unilateral seizures are part of the progression to full-blown amygdala-kindled seizures, preventing these earliest manifestations can prevent progression to a full-blown episode. The hope is that, by analogy, preventing the early subsyndromal symptoms of the affective disorders could preclude the emergence of full-blown affective episodes. Importantly, if the pharmacological dissociations revealed in the kindling model are pertinent to those in the affective disorders, the data indicate that different drugs are effective at different stages of disease progression. For example, drugs such as carbamazepine and lamotrigine, which are highly effective in preventing full-blown amygdala-kindled seizures, are not effective against the initial stages of kindling development.[2,4] Conversely, benzodiazepines, which prevent early- and mid-phase seizures, are not effective against late spontaneous ones, while phenytoin shows the opposite pattern. Thus, caution must be taken in inferring that drugs effective against full-blown manic or depressive episodes would necessarily be effective in the earliest phase of affective illness evolution.

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Box 1 Bipolar disorder is a multifaceted progressive illness

1. Episodes recur faster, with a shorter euthymic interval after each successive one.
2. Recurrent episodes require less precipitation by stressors (become more autonomous).
3. Medical and psychiatric comorbidities accumulate, including the likelihood of substance abuse.
4. Cognition deteriorates as a function of the number of previous episodes.
5. Prefrontal cortical neuroanatomical deficits increase.
6. Treatment refractoriness increases.
7. End-stage complications such as inadequate self-care and dementia may occur.
8. Loss of one or more decades of life expectancy occurs, more from cardiovascular disease than from suicide.

Types of sensitization in the mood disorders

Stress sensitization

There is a robust literature indicating that childhood adversities, particularly when followed by further stressors in adulthood, are prime candidates for precipitating affective episodes.[1,5] While many candidate gene-environmental interactions associated with this phenomena have not been replicated, the fundamental observations of stressors in childhood predisposing to affective episodes later in adulthood are consistent and highly replicable.[6] The bulk of these data are in unipolar depression, but also appear applicable to bipolar disorder, where childhood stressors are a clear-cut poor prognosis factor for early onset and a more adverse course of illness. Differences in types, timing, and duration of stressors may have important consequences for illness progression, but a history of verbal abuse (even in the absence of physical or sexual abuse) is associated with an early onset of bipolar disorder and a more adverse course of illness.[7] As multiple affective episodes occur, the vulnerability to further episodes increases and, as in kindling, spontaneous episodes also begin to occur. The occurrence of early stressors is also a vulnerability factor for later development of PTSD, and is a potent risk factor for animals and humans developing and sustaining substance abuse.[2,8]

Substance abuse sensitization

If animals are repeatedly given psychomotor stimulants, such as amphetamine or cocaine, they show progressive increases in motor activity and stereotypy in response to the same dose. This has an epigenetic mechanism, as revealed by the fact that the methylation inhibitor zebularine prevents sensitization.[9] Zebularine also prevents the effects of early-life stressors decreasing brain-derived neurotrophic factor (BDNF) in the prefrontal cortex, suggesting that some aspects of stress sensitization are also mediated by epigenetic mechanisms.[10] Epigenetic mechanisms are those associated with environmental events placing chemical tags on DNA, histones, and microRNA that can influence which genes are transcribed or inhibited.[2,3] There is a high incidence of substance abuse in patients with bipolar disorder, and when the two co-occur, the course of illness is more difficult based on the convergence of additional stressors, episodes, and bouts of substance abuse as well as their cross-sensitization.[11,12] BDNF increases are seen in the nucleus accumbens following defeat stress-induced sensitization, cocaine sensitization, and in humans with depression. There is also some evidence that early-onset bipolar disorder and substance abuse share some genetic vulnerabilities.[13]

Episode sensitization

In some individuals with unipolar or bipolar depression, repeated episodes occur on average with increasingly shorter euthymic intervals and increasing severity and treatment resistance.[10] Greater numbers of prior episodes are also associated with increasing cognitive dysfunction.[14] Two episodes of unipolar or bipolar depression do not increase the risk of a diagnosis of dementia in old age, while four episodes double this risk, and each additional episode thereafter further increases the risk.[15] Animal models of depression reveal epigenetic mechanisms underlying episode sensitization, and depressed individuals with histories of abuse in childhood have more epigenetic changes than those without such a history.[3,12,16] Subthreshold symptoms of depression and mania can also be precursors to the emergence of more full-blown episodes; for this reason, as well as the possibility that they also contribute to illness progression on a clinical or mechanistic (epigenetic) basis, the importance of preventing subthreshold symptoms is also emphasized.

Analogy to progressive somatic mutations in cancer evolution

In cancer development and progression (for colon, breast, and lung malignancies), there appears to be an accumulation of a series of somatic mutations, typically involving loss of protective oncogenes or tumor suppressive factors and increases in cellular proliferative factors. Further mutations are associated with tumor invasion and metastasis. It would appear that a similar pattern of progressive epigenetic changes drives illness progression in the recurrent affective disorders. While the somatic mutations seen in cancer do not occur in the mood disorders, changes in gene expression driven by epigenetic mechanisms convey losses in neuroprotective factors (the "good guys") and increases chemical alterations driving behavioral pathology (the "bad guys"). Each new episode tends to diminish the "good guys" and enhance the "bad guys," shifting the ratio toward episode occurrence and reduced levels of compensatory mechanisms, such as thyrotropin-releasing factor and GABA inhibition. As in cancer progression, early treatment is easier and less complicated than at later stages.[12]

Illness progression in the affective disorders (Box 1) appears to have multiple interacting mechanisms. There is evidence of neuroendocrine dysfunction, mitochondrial and oxidative stress, inflammation, and loss of neuroprotective factors.[14] Bipolar disorder should be viewed as a systemic illness affecting a wide variety of organs in the periphery and the brain. Among the most lethal is

proneness to cardiovascular disease, which is associated with loss of a decade or more in life expectancy.

Prefrontal cortex microanatomy and function begins to fail as dendritic length and complexity decreases, synapses regress, and adult mushroom-shaped spines revert to immature spike-shaped spines. These changes are seen on autopsy in the prefrontal cortex of depressed patients and in animal models of depression.

New data on the effects of ketamine are revealing. Not only does ketamine exert rapid-acting antidepressant effects in animals and humans, but its IV administration is associated with normalization of spine, synapse, dendrite, and prefrontal cortical communication deficits within a few hours.[17] This process appears to be vascular endothelial growth factor (VEGF)-dependent, as inhibiting VEGF wipes out the antidepressant effects of ketamine and administration of VEGF into the prefrontal cortex reproduces the positive effects seen with ketamine. This effect may interact with BDNF and with many other downstream intracellular pathways and mechanisms, as noted above.

Defeat stress as a model of peripheral inflammation affecting the central nervous system

The defeat stress model of depression reveals the importance of inflammatory mechanisms.[18,19] Repeated exposure to a larger, aggressive, home-cage mouse for 10 days results in the intruder mouse becoming depressed, asocial, and anhedonic (not preferring sugar water). If the secretion of IL-6 from white cells is blocked, the animals do not become depressed. In addition, if IL-6 secretion from monocytes in the bone marrow is prevented, animals do not become depressed. After a second bout of defeat stress, primed monocytes are stored in the spleen; if IL-6 is blocked from these cells, depression-like behaviors do not occur. It appears that the IL-6 secreted into the blood crosses the blood-brain barrier in endothelial cells, activates microglia, and starts a cascade of inflammatory effects that result in activation of inflammasomes, secretion of IL-1 beta, and other downstream neurobiological changes associated with depression. Multiple studies and meta-analyses have linked increases in markers of inflammation – particularly IL-1, IL-6, tumor necrosis factor (TNF)-alpha, and C-reactive protein (CRP) – with bipolar disorder, as recently reviewed by Fries et al.[20]

Increased vulnerability to child and adolescent bipolar disorder in the U.S. compared to Europe

Two-thirds of bipolar disorder cases in adults in the U.S. begin in childhood or adolescence (before age 19), while only one-third of cases begin this early in the Netherlands and Germany.[21-23] This appears to be based on increases in both genetic and environmental vulnerability in the U.S. Early-onset illness is associated with the additional risk factor of longer delay to first treatment, and early onset and treatment delay are both independent risk factors for a poor outcome in adulthood. While some have argued that these transnational differences could be attributed to diagnostic differences, this does not appear to be the case. In the study of Mesman et al.,[24] which

claimed a similar incidence in the U.S. and the Netherlands, the category of bipolar disorder not otherwise specified (BP-NOS) was not included in the assessment, and BP-NOS represents the highest proportion of children with early onset bipolar disorder. Moreover, children with bipolar disorder from the U.S. were more ill than those from the Netherlands in terms of increased numbers of comorbidities. In our cohort, adults with bipolar disorder in the U.S. were more ill than their European counterparts, and so were their offspring,[25,26] siblings, and spouses. In the 676 patients from the U.S. compared to the 292 from Europe, there was a significantly higher prevalence of anxiety disorders, alcohol abuse, substance abuse, rapid cycling, 20 or more prior episodes, and prospective nonresponders to naturalistic treatment, but fewer hospitalizations.[2] In addition, those from the U.S. have more obesity and a host or other medical problems compared to the Europeans.[27]

A bipolar spectrum disorder diagnosis occurs in 2.2% of adolescents in the U.S., yet only 20% of them are on any kind of treatment.[28] Thus, earlier recognition and treatment of youngsters with a bipolar spectrum diagnosis is urgently needed to stem the tide of multi-generational transmission of illness.[25,29] Axelson et al.[30] indicated that 74% of the offspring of a parent with bipolar disorder developed a major psychiatric diagnosis at 8 years of follow-up. The problems of early-onset illness will only continue to worsen as data indicate the presence of a cohort effect for depression, bipolar disorder, and substance abuse.[31,32]

High-risk individuals can be identified by presently available clinical characteristics

Genetic vulnerability is a crucial risk factor for the onset of bipolar disorder, and Stahl et al.[33] have identified 30 loci with genome-wide significance, but we are still a long way from being able to use genetics as a reliable predictor of bipolar disorder. However, if a positive family history of bipolar disorder in parents and grandparents is accompanied by a history of adversity in childhood, the likelihood of early-onset illness is further enhanced. If these two vulnerabilities are also accompanied by prodromal symptoms, risk is further amplified.[34] The ready identification of individuals at high and very high risk gives credence to efforts at early intervention and prevention. Many variables associated with good health can be introduced in high-risk individuals, including good diet, exercise, weight management, and sleep hygiene.[35] In those who are already prodromal, family-focused therapy (FFT) or one of its many closely aligned therapies is highly effective and should be offered more consistently.[36,37]

There are mixed data for omega-3-fatty acids helping to ward off a diagnosis of schizophrenia in those who are prodromal, and parallel studies should be conducted in bipolar disorder. The potential protective effects of safe and well-tolerated supplements – such as folate, vitamin D3, N-acetylcysteine, acetyl-L-carnitine, and phosphatidylcholine – all deserve to be further studied, but such studies are not given high priority or are being funded by the NIMH and other regulatory and funding bodies.

This should change based on both current need and clinical and theoretical support, but also on the basis that more formal neurobiological markers eventually will be found and replicated. When these markers become available, one would still need to proceed with studies of what types of primary and secondary prevention are effective in these high-risk individuals.

Consistent long-term prophylaxis required after the first manic episode

The types and consistency of intervention after the occurrence of a first manic episode needs major revision. Studies reveal the cognitive and structural deficits that occur with first mania are resolved over the next year only on the condition that no further episodes occur.[38,39] Preventing further episodes in the year after a first manic episode is no easy task, and the types and aggressiveness of treatment needed to achieve this end require further study.

One hint of an effective strategy would be the greater use of lithium. Berk et al.[40] reported that, in first-episode bipolar patients randomized to a year of lithium or quetiapine, those on lithium did better in every respect: fewer episodes of mania and depression, better functioning and cognition, and fewer abnormalities on brain imaging. Moreover, Hafeman et al.[41] found lithium superior to other mood stabilizers in long-term follow up, mirroring the results of Geller et al.[42] and the findings of Goldstein et al.[43] that treatment with lithium resulted in fewer patients acquiring substance-abuse comorbidities.

One of the strongest studies supporting the need for early, comprehensive, long-term specialty treatment is that of Kessing et al.[44] They randomized adolescents and young adults with a manic hospitalization to receive 2 years of comprehensive specialty clinic treatment or treatment as usual (TAU) in the community, which, in the study setting of Denmark, is free and usually of exceptionally high quality. Those randomized to the specialty clinic not only had fewer relapses over the next 2 years, but this continued over a total of 6 years, even though all patients had returned to TAU after the first 2 years. Specialty-clinic treatment included psychotherapy, pharmacotherapy, psychoeducation, mood charting, and recognition of early symptoms that might signal a relapse. One can conclude that early comprehensive treatment can moderate the long-term course of bipolar disorder and change it for the better. However, making such comprehensive treatment available to every patient with bipolar disorder will require massive shifts in medical and public health practice in the U.S. and elsewhere.[23,35]

Early treatment may require judicious complex combinations to achieve and maintain remission

Many texts and treatment guidelines emphasize the use of monotherapy as a sufficient approach to bipolar disorder. However, in controlled studies of pharmacoprophylaxis, remission is rarely achieved with monotherapy, and more complex regimens typically need to be utilized and further studied. Viral load in HIV/AIDS cannot be reduced to negligible levels without triple antiviral therapy, and the complexity of pharmacological treatment required to maintain bipolar disorder patients requires further study. As in HIV/AIDS, more complex combination treatments targeting different transmitter systems may be required.

We already know from studies measuring reduction in bipolar illness reoccurrence that combination therapy is consistently more effective than monotherapy. Such systematic combination studies include those of lithium and valproate; lithium and carbamazepine; lithium and lamotrigine; lithium and nimodipine; quetiapine and lamotrigine; and all of the anticonvulsants as augmented by atypical antipsychotics.[23,35,45] What other supplements and drugs need to be added to achieve and maintain the desired goal of remission is not known, but should be a high priority for further study.

In the absence of a large body of systematic data,[35] one needs to be extremely careful when instituting complex treatment regimens, using slow, incremental dose escalation of each new agent; titrating effectiveness against the emergence of any side effects is crucial to achieving an efficacious and well-tolerated regimen. Patients should be encouraged to conduct systematic daily life charting of mood, medications, and side effects, which may be particularly important in achieving an optimal regimen. Personal calendars and mood charts can be copied from Post & Leverich[45] or downloaded from www.bipolarnews.org (click on mood chart or personal calendar).

Later stages of illness require more complex treatment

We can try to ameliorate many of the episode-driven difficulties with cognition and function by engaging in more optimal treatment of bipolar illness from the outset. However, a great many patients already present with multiple episodes, cognitive dysfunction, and treatment resistance, and these later-stage characteristics need to be dealt with aggressively.[3,23,45,46] In many instance, this is likely to involve multiple medications[2] (almost all off-label) targeting the medical and psychiatric comorbidities that commonly accompany bipolar disorder (Box 2).

Box 2 Drugs targeting multiple comorbidities in bipolar disorder

N-acetylcysteine (NAC)	Acetyl-L-carnitine (ACL)	
Cocaine	Pain	
Alcohol	Insulin receptor sub-sensitivity	
Nicotine	Peripheral neuropathy	
Marijuana; gambling	Hypertension	
OCD; PTSD; trichotillomania		
Depression; autism		
Valproate (VPA)	Topiramate	Zonisamide
Migraine	Alcohol; cocaine	Alcohol
Anxiety	Bulimia; migraine	Bulimia
Alcohol	Anger attacks	
Gabapentin (GPN)	Modafinil	
Anxiety; social phobia	Cocaine: narcolepsy; ADHD	
Alcohol; pain		

When combinations are administered carefully, their side-effect burden can even be lower than when trying to achieve a complete response with high doses of a single substance. Comorbid anxiety and substance abuse complicate treatment, need to be addressed specifically, and will usually require further medications. Similarly, diabetes, obesity, and other elements of the metabolic syndrome often accompany bipolar disorder, and, along with smoking, convey a great risk for early loss of life expectancy, primarily because of cardiovascular disease.[47] Treatment and prevention of the comorbidities of bipolar disorder require specific attention and will often mandate increasingly complex approaches.

Conclusions

Bipolar disorder is a progressive, potentially lethal medical illness that all too often is not given the attention and respect that is required to moderate its course. Like a malignancy that is not adequately dealt with in a timely fashion, bipolar disorder can progressively evolve to a more treatment-refractory and pernicious stage. Such a progression can involve the accumulation of and sensitization and cross-sensitization to stressors, mood episodes themselves, and bouts of substance abuse. Each of these appears to have underlying neurobiological mechanisms driven by epigenetic changes in DNA, histones, and microRNA. Since these are environmentally driven changes, they are amenable to efforts at prevention and treatment. Early attempts at stress reduction and modulation, as well as episode and substance abuse treatment and prevention, would appear to be critical to preventing a malignant transformation of bipolar disorder from a manageable illness to an incapacitating and treatment-resistant one.

A new round of research, academic, and public health attention will be required to more adequately and properly treat this illness. Given the likelihood that this will not be readily achieved in the near future, it behooves each physician to attempt to provide the type of early and comprehensive treatment that Kessing et al.[44] documented as essential to a more benign outcome.

Disclosure

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