Heading off depressive illness evolution and progression to treatment resistance

Robert M. Post, MD

Abstract

Viewing recurrent depression as a potentially progressive illness may help transform treatment toward earlier, more consistent intervention and prevention. Evidence indicates that recurrent stressors, episodes of depression, and bouts of substance abuse can each show sensitization (increased reactivity upon repetition) and cross-sensitization to the others, and drive illness progression and treatment resistance. These long-lasting increases in pathological responsivity appear to be mediated by epigenetic mechanisms involving alterations in chemical marks placed on DNA and histones. These types of sensitization effects are amenable to clinical attempts at amelioration and prevention, and provide treatment targets and strategies to minimize the likelihood of illness progression to treatment resistance.

Keywords: *behavioral sensitization; kindling; stressor; epigenetics; pharmacoprophylaxis*

Author affiliations: George Washington University School of Medicine, Washington, DC, USA; Bipolar Collaborative Network, Bethesda, Maryland, USA

Address for correspondence: Robert M. Post, MD, Bipolar Collaborative Network, 5415 W. Cedar Lane, Suite, 201-B, Bethesda, MD 20814, USA (e-mail: robert.post@speakeasy.net)

Introduction

In examining causes of and approaches to difficult-to-treat and refractory mood disorders, it is important to review several of the potential and correctable mechanisms involved. One, disappointingly, still involves stigma; people do not take depressive illness seriously enough. Therefore, too few people with major depression are in treatment; treatment is often not early, aggressive, or persistent enough; and prophylaxis not maintained as necessary for those with several prior recurrences. Episodes recur, stressors accumulate, and substance abuse and medical comorbidities become more likely, each contributing to an evolution in illness severity, complexity, and poor response to subsequent treatment, ie, a type of acquired treatment resistance.

Sensitization and kindling-like processes

Thus, inadequate treatment and prophylaxis itself generates treatment resistance. Depressive episodes beget further episodes and more rapid relapses.[1,2] One could view this as sensitization or increased vulnerability to recurrence. Stresses are often involved in the precipitation of initial episodes of an individual's illness, and one can become sensitized to recurrent stressors to the point where more trivial stressors are sufficient triggers.[1,3,4] Following enough successive recurrences, triggering by stressors continues but is less necessary, and episodes also begin to occur more autonomously.[5-7] This follows a course similar to that observed with electrical kindling of the amygdala in which behavioral, biochemical, and physiological responses to each daily, brief, 1-second stimulation increase in magnitude and duration until full-blown seizures develop in response to a previously subthreshold stimulation.[8] Then, following enough stimulations, spontaneous seizures begin to occur in the absence of stimulation.[9] In a similar fashion there can be sensitization to both recurrent stressors[10,11] and to episode recurrence.[12]

In addition, the affective disorders are often complicated by alcohol and substance abuse, in which behavior sensitization (increased responsivity) again occurs and is well documented in animals and humans.[13] These sensitization processes (to stressors, episodes, and abused substances) can not only drive illness progression in their own right, but evidence suggests that each can cross-sensitize to the other two processes yielding a vicious cycle or positive feedback path of increasing illness exacerbation.[13,14]

Given this potential for illness evolution and progression, one of the critical interventions would be early institution of treatment and effective pharmacoprophylaxis. Too often, even acutely effective treatment is discontinued and prevention not pursued, with potentially grave consequences. Depression is the number one cause of disability worldwide, and the personal, social, and economic consequences can be devastating. In the United States the excess medical mortality of patients with serious mental disorders is enormous (of the order of magnitude of 1 to 2 decades) and cardiovascular illness is a

much greater cause of loss of years of life expectancy than directly illness-related death by suicide.[15,16]

An examination of some of the mechanisms involved in these aspects of illness progression may give further weight to their wider public consideration and associated efforts at earlier and more effective intervention.

Neurobiological mechanisms underlying illness progression

Epigenetic memory-like effects

The presence of sensitization and kindling-like processes yielding an increased responsivity to repetition of stressors, episodes, and abused substances indicate that a memory-like mechanism must be involved. We had previously postulated long-term changes in gene transcription as an important component of these aspects of illness progression.[1] More recently it has become clear that epigenetic mechanisms are the mediators of these long-term changes in responsivity.[3,4,13] Epigenetic literally means "above genetics" and refers to environmentally induced changes in DNA form and structure but not in sequences mediating inherited traits. For example, DNA can be methylated, typically yielding the nearby genes less likely to be transcribed. DNA is wound around histones, and chemical changes in histones, such as acetylation, make DNA less tightly wound and more amenable to gene transcription. Conversely, histone methylation typically yields more tightly wound DNA, which is usually associated with inhibition of gene transcription.[17] Many other environmentally induced changes in DNA and histones also occur, but these are among the most common, along with changes in micro-RNA that can further alter what proteins get synthesized or not.

The changes in DNA and histone acetylation and methylation are long-lasting but not immutable, and can be altered by a large variety of enzymes that facilitate or inhibit these epigenetic modifications. One example of the long-lasting effects of early adversity is the finding of Roth et al[18] that poor maternal care in the first 10 days of a rat pup's life results in life-long decreases in brain-derived neurotrophic factor (BDNF) in the frontal cortex. The adverse experiences cause the promoter region of DNA to be methylated, thus turning down transcription of the BDNF gene and translation into new BDNF protein. If a methylation inhibitor, zebularine, is given early in life, the BDNF deficits do not occur.[18]

Stressors in adulthood also cause epigenetic changes in BDNF and other substances. Repeated episodes of defeat stress can induce depression-like behavior and social avoidance in animals, which also have an epigenetic basis.[17] Likewise, cocaine sensitization is mediated by epigenetic changes and can be prevented by pretreatment with the methylation inhibitor zebularine.[19] Data in animals and humans indicate that BDNF is decreased in hippocampus and increased in the nucleus accumbens (NAc) by repeated stressors, depressive-like episodes of defeat stress, and also in human clinical depression in those who have died by suicide.[20]

It appears as if these abnormal reactivities and behaviors are being overlearned in the ventral striatum (NAc), and with increasing repetition are also being transferred to the habit memory system of the dorsal striatum.[13,21] New data further indicate that more traditional or psychological types of learning and memory are also mediated by epigenetic changes.[22,23] Conscious or representation memory processes typically have their basis in structures of the medial temporal lobe—amygdala and hippocampus—and ultimately the cerebral cortex.[24] However, the habit memory system of the striatum functions on an unconscious basis and would appear to be the reason that so many pathological habits and addictions are resistant to traditional dynamic psychotherapies fostering insight or other more focused attempts at extinction.[13,21] The habit memory system seems to have a mind of its own, generating automatic, autonomic, and compulsive behavioral responses even after an individual believes that they are free from drug craving or pathological impulses.

In parallel with the animal studies, greater epigenetic changes have been found in brain of patients who committed suicide and also had histories of early-life adversity compared with those without such traumatic experiences.[25-27] Thus, evidence is mounting that life experiences with recurrent stressors, episodes of depression, and bouts of substance abuse are causing a vast array of accumulating epigenetic pock marks.[3,4] Since many of these are associated with sensitization, pathological, and interacting effects, the potential for progressive and acquired increases in illness, severity, complexity, and refractoriness is high.

Passive and allostatic alterations

In addition to these active, pathologically learned overreactivities involving memory-like processes, there are

an array of other more generalized processes yielding increases in brain and somatic abnormalities that further contribute to illness progression.

These can involve increases in oxidative stress, inflammation, and mitochrondrial dysfunction. When the brain and body attempt to compensate for pathological neurobiological alterations, new sets of adaptions are brought into play in an attempt to reestablish homeostasis. This attempt at adaptation and compensation often involves the establishment of a new set point of equilibrium, which comes at a cost and is considered an increase in the body's allostatic load.[28,29] This increase in allostatic load can have pathological consequences, driving increases in psychological and somatic abnormalities and contributing to illness progression.

A particularly robust example is the effects of stressors and maladaptive behaviors on telomeres. Telomeres are the DNA strands that cap the ends of DNA and protect the precision of DNA replication. Telomeres shorten with each cell replication and shorter telomeres are associated with aging. The percentage of shorter telomeres that one has is associated not only with aging and processes of senescence, but with increased liability to a very wide range of medical and psychiatric illnesses. Adversity in early life is associated with shorter telomeres as is an increasing number of depressive episodes.[30-33] Many of the common accompaniments of depression are associated with shorter telomeres, including poor diet, a lack of exercise, and a lack of mindfulness/meditation or the feeling that one is making a positive contribution to others in accomplishing one's life goals. Interestingly, nihilistic and pervasive anger is also associated with shorter telomeres. Lithium directly increases the enzyme telomerase, which adds to telomere length,[34] so augmentation of antidepressants with lithium may have a triple benefit of: (i) preventing episode recurrence; (ii) increasing telomere length; and (iii) increasing BDNF and neurogenesis with consequent increases in hippocampal and cortical volume.

Neuroprotective factors such as BDNF and vascular endothelial growth factor (VEGF) decrease with every episode of depression, further leaving the brain and body vulnerable to illness-associated oxidative stress, mitochondrial dysfunction, and inflammation. Thus, these passive mechanisms, along with shortening of telomeres, add to and combine with whatever active sensitization and memory-like mechanisms exist to drive illness toward a progressively more vulnerable and pathological neurobiological and somatic state of poor health.

Therapeutic and public health implications

One obvious place to start to change the treatment paradigm is to make some of these facts more widely known to the general public and more widely acted upon by psychiatrists and general practice physicians. This will likely require whole new processes of public education. Newspapers and popular magazines not only have recently failed to convey adequate information, but often appear more interested in distorting and sensationalizing medial and conflict-of-interest stories for the sake of increased circulation. For example the overwhelming data about the benefit of continuation of antidepressant treatment in responders compared with discontinuation with placebo is virtually never cited in recent publications, which instead only mention the fact that acute antidepressant treatment efficacy sometimes doses not exceed that of placebo by a large margin. The inferred take-home message for the public is that antidepressants don't work very well. Neglected are the findings that there is an amazing 75% reduction in depressive recurrences with antidepressant continuation[35] and that the statistical significance of the findings are astronomically large. Similarly the fact that virtually all antidepressant modalities increase BDNF and neurogenesis is rarely mentioned, nor are the important findings of Sheline et al[36] that longer, compared with briefer, exposure to antidepressants is associated with a preservation of hippocampal volume. Patients need to explicitly hear and understand the message that has been around for decades that every medical organization and treatment guideline (of which we are aware) has endorsed the ideal of long-term prophylactic treatment after several prior depressive episodes. Long-term (lifelong) treatment of hypertension or high cholesterol to prevent recurrence of cardiovascular crises is widely known, accepted, and practiced; preventive treatment of recurrent depression needs to have the same cachet. Similarly, making the data on depressive illness progression and the severity of the personal and medical consequences better known so that patient can make better-informed decisions is a must.

Depression also has transgenerational consequences, by both the genetic and epigenetic routes. The children of mothers whose depression is treated to remission have fewer behavioral problems and psychiatric diagnoses than those whose depression is only partially improved.[37]

Intrauterine exposure to a mother's depression, as well as postpartum depression, also has consequences for the offspring. Postpartum depression occurs in 15% of unselected women and at a much higher rate in those with prior depression. All women should be screened for postpartum depression and offered, in the most supportive fashion possible, appropriate treatment and ongoing support until they are well. Fathers' depression is also not without consequence to the offspring, conveyed both by traditional conceptions of altered interactions with the child yielding social, endocrine, and neurobiological consequences, but also by a newly discovered route where the fathers' environmental experiences with stressors or drugs of abuse can affect the offspring (even in the absence of paternal parental contact) presumably by epigenetic changes that are transmitted via sperm.[38,39] Even grandparental history of depression may play a role, as a history of depression in the grandparents conveys a markedly increased vulnerability to depression in the third generation, compared with a parental history of depression alone.[40]

In addition to these genetic and epigenetic mechanisms of illness vulnerability and transmission are the wider societal changes and other factors that somehow confer cohort and anticipation effects.[41] Every birth cohort since World War I has had an increased incidence and early age of onset of both unipolar and bipolar depression. Understanding and approaching some of the potential mediators of these effects such as increases in substance abuse and in child abuse may also be valuable.

Finally, using a staging concept of illness evolution may help change the treatment paradigm to earlier and more consistent preventive intervention.[42,43] One already knows many clinical risk factors for depression, and neurobiological markers are also beginning to be revealed. Thus, one could consider this at-risk status as Stage I – Vulnerability, Stage II – Well Interval, and Stage III – Prodrome, which may also offer opportunities for early intervention and prevention instead of the conventional delayed mode of treatment that typically occurs after Stage IV – Full Syndrome, Stage V – Recurrence, and Stage VI – Progression. We have already seen that treatment is more difficult and complicated in these stages and in the later Stage VII – Treatment Refractoriness, which is too often followed by Stage VIII – Late or End Stage Illness associated with cognitive impairment, medical complications, incapacitation, and need for supervised care. Bipolar illness appears more pernicious in the US than in many European countries,[44] and it is likely that many of the same genetic and environmental mechanisms would similarly influence the course of unipolar depression.

In treatment approaches to malignancies the illness is staged to help with appropriate treatment, and no one would never endorse a wait-and-see attitude to observe whether a primary lesion grows in size, invasiveness, and aggressiveness, metastasizing to distant locations and becoming increasingly treatment-resistant. One may counter this view with the argument that malignant transformation in cancer is very different from that in depression and highly lethal. However, the potential lethality of depression by suicide and increased medical mortality can be equally devastating, and analogies to cancer evolution are not without some merit. In cancer evolution there are progressive increases in the number of somatic mutations generating increases in oncogenic cell survival and multiplication factors and, concomitantly, decreases in tumor suppressor factors.[45] In late stages very complex medication strategies are required to induce tumor regression and prevent drug tolerance and re-emergence of the malignancy.

In recurrent depressive illness, there is not an accumulation of somatic mutations but rather of epigenetic alterations or pockmarks (what some have called epimutations). These need to be treated with the same respect as the potential of a benign lesion transforming to a malignant one in carcinogenesis involving enhancement cell cycle promoters and loss of tumor suppressor factors. In malignant transformation, the "bad guys" of cell proliferation overwhelm the diminishing "good guys" of tumor suppressor factors. In a parallel fashion many of the epigenetic pockmarks of recurrent depressive disorder are associated with progressive increases in primary pathological processes driving the illness (the bad guys) such as increases in corticotropin-releasing factor and in BDNF in the NAc and habit memory system, in conjunction with loss of adaptive and neuroprotective factors (the good guys) such as failure of thyrotropin-releasing hormone to increase and BDNF decrements in hippocampus and prefrontal cortex.[1,3,46,47]

Personal treatment strategies, public health measures, and education each require a major paradigm shift toward earlier and more effective long-term treatment. Hopefully that will help prevent the multiplicity of acquired untoward effects of depressive illness and its tendency to progress to more complex and treatment resistant forms, as is all too frequently the case with current clinical practice. ❑

REFERENCES

1. Post RM. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *Am J Psychiatry.* 1992;149(8):999-1010.
2. Kessing LV, Andersen PK. Does the risk of developing dementia increase with the number of episodes in patients with depressive disorder and in patients with bipolar disorder? *J Neurol Neurosurg Psychiatry.* 2004;75(12):1662-1666.
3. Post RM. Preventing sensitization and kindling-like progression in the recurrent affective disorders. In: Chiccetti D, ed. *Developmental Psychopathy.* In press.
4. Post RM. The kindling/sensitization model and the pathophysiology of bipolar disorder. In: Soares J, Young A, eds. *Bipolar Disorders: Basic Mechanisms and Therapeutic Implications*. In press.
5. Kendler KS, Thornton LM, Gardner CO. Stressful life events and previous episodes in the etiology of major depression in women: an evaluation of the "kindling" hypothesis. *Am J Psychiatry.* 2000;157(8):1243-1251.
6. Kendler KS, Thornton LM, Gardner CO. Genetic risk, number of previous depressive episodes, and stressful life events in predicting onset of major depression. *Am J Psychiatry.* 2001;158(4):582-586.
7. Slavich GM, Monroe SM, Gotlib IH. Early parental loss and depression history: associations with recent life stress in major depressive disorder. *J Psychiatr Res.* 2011;45(9):1146-1152.
8. Goddard GV, McIntyre DC, Leech CK. A permanent change in brain function resulting from daily electrical stimulation. *Exp Neurol.* 1969;25(3):295-330.
9. Pinel JP. Effects of diazepam and diphenylhydantoin on elicited and spontaneous seizures in kindled rats: a double dissociation. *Pharmacol Biochem Behav.* 1983;18(1):61-63.
10. Antelman SM. *Stressor-induced Sensitization to Subsequent Stress: Implications for the Development and Treatment of Clinical Disorders*. Caldwell, NJ: Telford Press; 1988.
11. Caspi A, Sugden K, Moffitt TE, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science.* 2003;301(5631):386-389.
12. Kessing LV, Mortensen PB, Bolwig TG. Clinical definitions of sensitisation in affective disorder: a case register study of prevalence and prediction. *J Affect Disord.* 1998;47(1-3):31-39.
13. Post RM, Kalivas P. Bipolar disorder and substance misuse: pathological and therapeutic implications of their comorbidity and cross-sensitisation. *Br J Psychiatry.* 2013;202(3):172-176.
14. Covington HE, 3rd, Miczek KA. Repeated social-defeat stress, cocaine or morphine. Effects on behavioral sensitization and intravenous cocaine self-administration "binges". *Psychopharmacology.* 2001;158(4):388-398.
15. Colton CW, Manderscheid RW. Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. *Prev Chronic Dis.* 2006;3(2):A42.
16. Newcomer JW, Hennekens CH. Severe mental illness and risk of cardiovascular disease. *JAMA.* 2007;298(15):1794-1796.
17. Nestler EJ. Epigenetic mechanisms of depression. *JAMA Psychiatry.* 2014;71(4):454-456.
18. Roth TL, Lubin FD, Funk AJ, Sweatt JD. Lasting epigenetic influence of early-life adversity on the BDNF gene. *Biol Psychiatry.* 2009;65(9):760-769.
19. Anier K, Zharkovsky A, Kalda A. S-adenosylmethionine modifies cocaine-induced DNA methylation and increases locomotor sensitization in mice. *Int J Neuropsychopharmacol.* 2013;16(9):2053-2066.
20. Krishnan V, Han MH, Graham DL, et al. Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions. *Cell.* 2007;131(2):391-404.
21. Mitchell MR, Weiss VG, Beas BS, Morgan D, Bizon JL, Setlow B. Adolescent risk taking, cocaine self-administration, and striatal dopamine signaling. *Neuropsychopharmacology.* 2014;39(4):955-962.
22. Day JJ, Sweatt JD. Epigenetic mechanisms in cognition. *Neuron.* 2011;70(5):813-829.
23. Zovkic IB, Guzman-Karlsson MC, Sweatt JD. Epigenetic regulation of memory formation and maintenance. *Learn Mem.* 2013;20(2):61-74.
24. Mishkin M, Appenzeller T. The anatomy of memory. *Scientific American.* 1987;256(6):80-89.
25. McGowan PO, Sasaki A, D'Alessio AC, et al. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nat Neurosci.* 2009;12(3):342-348.
26. Labonte B, Suderman M, Maussion G, et al. Genome-wide methylation changes in the brains of suicide completers. *Am J Psychiatry.* 2013;170(5):511-520.
27. Mehta D, Klengel T, Conneely KN, et al. Childhood maltreatment is associated with distinct genomic and epigenetic profiles in posttraumatic stress disorder. *Proc Natl Acad Sci U S A.* 2013;110(20):8302-8307.
28. McEwen BS. Allostasis and allostatic load: implications for neuropsychopharmacology. *Neuropsychopharmacology.* 2000;22(2):108-124.
29. Kapczinski F, Vieta E, Andreazza AC, et al. Allostatic load in bipolar disorder: implications for pathophysiology and treatment. *Neurosci Biobehav Rev.* 2008;32(4):675-692.
30. Epel ES, Blackburn EH, Lin J, et al. Accelerated telomere shortening in response to life stress. *Proc Natl Acad Sci U S A.* 2004;101(49):17312-17315.
31. Elvsashagen T, Vera E, Boen E, et al. The load of short telomeres is increased and associated with lifetime number of depressive episodes in bipolar II disorder. *J Affect Disord.* 2011;135(1-3):43-50.
32. Entringer S, Epel ES, Kumsta R, et al. Stress exposure in intrauterine life is associated with shorter telomere length in young adulthood. *Proc Natl Acad Sci U S A.* 2011;108(33):E513-518.
33. Wolkowitz OM, Mellon SH, Epel ES, et al. Leukocyte telomere length in major depression: correlations with chronicity, inflammation and oxidative stress--preliminary findings. *PloS One.* 2011;6(3):e17837.
34. Martinsson L, Wei Y, Xu D, et al. Long-term lithium treatment in bipolar disorder is associated with longer leukocyte telomeres. *Transl Psychiatry.* 2013;3:e261.
35. Geddes JR, Carney SM, Davies C, et al. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. *Lancet.* 2003;361(9358):653-661.
36. Sheline YI, Gado MH, Kraemer HC. Untreated depression and hippocampal volume loss. *Am J Psychiatry.* 2003;160(8):1516-1518.
37. Wickramaratne P, Gameroff MJ, Pilowsky DJ, et al. Children of depressed mothers 1 year after remission of maternal depression: findings from the STAR*D-Child study. *Am J Psychiatry.* 2011;168(6):593-602.
38. Bale TL. Lifetime stress experience: transgenerational epigenetics and germ cell programming. *Dialogues Clin Neurosci.* 2014;16(3):297-305.
39. Szutorisz H, DiNieri JA, Sweet E, et al. Parental THC exposure leads to compulsive heroin-seeking and altered striatal synaptic plasticity in the subsequent generation. *Neuropsychopharmacology.* 2014;39(6):1315-1323.
40. Weissman MM, Wickramaratne P, Nomura Y, et al. Families at high and low risk for depression: a 3-generation study. *Arch Gen Psychiatry.* 2005;62(1):29-36.
41. Lange KJ, McInnis MG. Studies of anticipation in bipolar affective disorder. *CNS Spectr.* 2002;7(3):196-202.
42. Post RM. Clinical staging in bipolar disorder: A historical perspective. In: Kapczinski F, ed. *Staging in Bipolar Illness?* Oxford, UK: Oxford University Press. In press.
43. Post RM, Fleming J, Kapczinski F. Neurobiological correlates of illness progression in the recurrent affective disorders. *J Psychiatr Res.* 2012;46(5):561-573.
44. Post RM, Altshuler L, Kupka R, et al. More pernicious course of bipolar disorder in the United States than in many European countries: implications for policy and treatment. *J Affect Disord.* 2014;160:27-33.
45. Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA, Jr., Kinzler KW. Cancer genome landscapes. *Science.* 2013;339(6127):1546-1558.
46. Post RM. Kindling and sensitization as models for affective episode recurrence, cyclicity, and tolerance phenomena. *Neurosci Biobehav Rev.* 2007;31(6):858-873.
47. Post RM. Animal models of mood disorders: Kindling as model of affective illness progression. In: Schachter SC, Trenite DG, eds. *Behavioral Aspects of Epilepsy: Principles and Practice*. New York, NY: Demos; 2008.