See article by Figueroa et al

Acquainted With the Night Again and Again: Key Factors Associated With Relapse in Major Depressive Disorder

Antolin M. Llorente, PhD[a,*]

I have been one acquainted with the night.
I have walked out in rain—and back in rain.
I have outwalked the furthest city light.

—Robert Frost, "Acquainted With the Night"

Major depression is one of the most prevalent neuropsychiatric disorders in the United States with significant morbidity, and in 2012 approximately 16 million adults 18 years and older experienced at least 1 major depressive episode.[1] According to the World Health Organization, major depression is also considered the disease that carries the heaviest disability burden among all neurobehavioral disorders, and it accounts for approximately 8.3% of all US years lived with a disability.[2] Unfortunately, as noted by Figueroa et al[3] in this issue of the *Journal*, the challenge of preventing relapse in major depressive disorder (MDD) may be greater than treating acute episodes, particularly given the fact that MDD relapse becomes progressively more frequent over time in individuals, with decreasing remission duration.[4] In addition, Mueller et al[5] noted that the rate of MDD relapse is quite high, as high as 80%, and that relapse is common, even during events in which a modifier such as postpartum depression is used in MDD.[6,7] Such a high relapse rate may be the result of lack of treatment efficacy responsible for residual symptoms or other factors not properly addressed for a large percentage of patients with a first and recurrent major depressive episode. At an experiential and personal level, our patients frequently tell us that the recurring nature of MDD takes an overwhelming toll on their emotional and adaptive well-being, which makes MDD feel like other highly debilitating, chronic medical conditions. The question then arises, What variables have been investigated as potentially responsible or representing enhanced risk for MDD relapse?

Research Focus to Date

Two variables have received significant attention in the scientific literature as potential causative factors in the recurrence of MDD, namely, dysfunctional cognitions and cognitive reactivity. Unfortunately, the peer-reviewed literature has equivocated as to which of these 2 factors is the dominant or key element responsible for increased risk of MDD relapse.[3] Figueroa et al[3] replicated previous findings suggesting that cognitive reactivity, not dysfunctional cognitions, represents a key risk factor for relapse in MDD. Furthermore, there is a need to understand what specific factors within cognitive reactivity are actually responsible for MDD relapse in order to advance the field. Figueroa et al[3] successfully provide such data, adding to the scientific literature. They note, using the Leiden Index of Depression Sensitivity-Revised, without requiring the use of mood induction paradigms, that *rumination*, in particular, may be significantly responsible for elevated levels of cognitive reactivity and indirectly responsible for increased risk of MDD relapse. This finding would be consistent with prior research.[8] Additionally, there may be intervening variables, or other factors altogether, in addition to or independent of cognitive reactivity, that, when primed, impact relapse in MDD.

Whether cognitive reactivity, by itself or in combination with other phenomena known to impact MDD relapse (eg, severity of first episode, full vs partial remission), and various other mediating and moderating factors yet to be discovered increases the risk of relapse in MDD, recurrence in MDD appears to be far more complex than what our research is able to elucidate at this time. For example, in a recent study, van Rijsbergen et al[9] suggest that mood reactivity, not cognitive reactivity, is the essential risk factor in MDD relapse. In their study,[9] mood reactivity was able to predict time to relapse over the course of 5.5 years, and cognitive reactivity failed to emerge as a risk factor for MDD relapse. However, increments in mood reactivity in combination with cognitive reactivity over time also predicted time to MDD relapse, as if acting synergistically. Given the current state of the literature, where should future research propel and direct us in the study of MDD relapse?

Future Directions

Thus far, we have benefited from Beck's[10] cognitive theory of depression, partially leading to the study of cognitive aspects of depression and its relapse; the contributions of Schildkraut,[11] viewing affective disorders partially as the result of aberrant levels and interrelationships among neurotransmitters and emphasizing the importance of pharmacotherapy adherence in relapse; and Teasdale's[12] postulates related to the cognitive aspects of relapse in MDD. However, as we enter the 21st century, we must move beyond past research and its replications. It behooves

[a]Department of Psychiatry, College of Medicine, Penn State Hershey and Milton S. Hershey Medical Center, Hershey, Pennsylvania

*Corresponding author: Antolin M. Llorente, PhD, Department of Psychiatry, Penn State Hershey, 500 University Drive, Hershey, PA 17033 (allorente@hmc.psu.edu).

J Clin Psychiatry 2015;76(10):e1315–e1317
dx.doi.org/10.4088/JCP.14com09743

us to comprehensively and systematically investigate the causes of recurrent MDD in greater detail, with increased specificity and scrutiny, and the study by Figueroa and colleagues[3] represents charter research in such a direction, but only in one aspect of MDD relapse. Therefore, a more comprehensive and detailed examination related to MDD relapse should incorporate other important elements, including its neuropathophysiology and its complex relapse mechanisms, in addition to continued investigation of its cognitive characteristics, since all of these factors impact its neurobehavioral expression and have potential treatment implications. Increasing evidence additionally suggests that depression and many of its characteristics, including its recurring nature, may be the result of far more complex brain-behavior relationships than our current understanding affords us. As a case in point, relatively recent studies using neuroimaging (functional magnetic resonance imaging [fMRI]) suggest that mood-related responses in afferent and efferent medial prefrontal cortex (mPFC) circuits and centers may be predictive of relapse in MDD, providing initial clues in terms of its neuropathophysiology.[13] However, additional research has demonstrated that other central nervous system areas and circuits may be involved, and this field of study requires further investigation and clarification.[14]

Another promising line of research that merits investigational attention and economic resources suggests that inflammatory mechanisms, in conjunction with specific genetic factors such as inflammatory cytokines, contribute to the development of depression in healthy and medically ill individuals and, in all likelihood, to its pernicious recurrence.[15–17] In fact, extensive research has now demonstrated that episodes of MDD may be related to protracted, low-level inflammatory mechanisms and related activation of cell-mediated immunity, as well as the onset of counteracting anti-inflammatory reflex mechanisms characterized by adverse immunoregulatory processes partially responsible for MDD relapse.[17,18] In addition, it has now been shown that episodes of MDD are accompanied by increasing nitrosative and oxidative stress and autoimmune responses directed against oxidative and nitrosative neoepitopes.[18,19] Such findings should not be surprising, because cytokines are critical for normal brain functions and have been shown to influence neuronal circuits and neurotransmitter systems to produce neurobehavior, both normal and abnormal. In addition, the scientific literature has demonstrated that long-term exposure to elevated inflammatory cytokines and protracted alterations in neurotransmitters can lead to neuropsychological disorders, including MDD.[19] Just as critical, inflammatory cytokines probably act as mediators of genetic and environmental interactions in the form of polymorphisms and may be related to MDD onset and relapse.

Although caution is required in their interpretation as a result of their representation as experimental analogs of MDD, research using animal models has also discovered that depression may be related to prolonged, low-grade inflammatory responses and subsequent activated cell-mediated immunity responses, as well as compensatory anti-inflammatory mechanisms, as is the case with humans. Such inflammatory mechanisms have been shown to be associated with increases in oxidative and nitrosative levels as a result of stress, contributing to neuroprogression in the onset of MDD-like behaviors, and probably to depressive relapse, consistent with literature in human studies. In animals undergoing experimental paradigms, such as immobilized stress or isolation from peers, experimental evidence has emerged that shows increases in central nervous system levels of proinflammatory cytokines with significant increases in levels of interleukin-1 (mRNA) in the brain[20] and behaviors similar to those in MDD in humans. In summary, inflammatory mechanisms, together with mood reactivity, may lead to significant risk capable of causing MDD relapses. However, not all individuals who experience MDD relapse (or a first MDD episode) carry such genetic risk and/or immune and damaging compensatory profiles. Hence, the relationship between cognitive reactivity and other cognitive and emotional factors associated with relapse in MDD may be far more complex than any one specific line of research alone may be able to elucidate to such an extent that relapse in MDD is most likely mediated by the interaction among genetic, environmental, and other risk factors, along with immune system (systemic and central nervous system) dysregulation.

In conclusion, in spite of significant effort, major depression continues to represent one of the most prevalent neuropsychiatric illnesses with significant morbidity. Research addressing selected cognitive and emotional aspects of MDD has revealed a complex interaction between cognitive reactivity and MDD, with diminishing risk attributed to dysfunctional cognitions as an important risk factor in relapse. The literature has also begun to indicate that specific characteristics of cognitive reactivity may actually be a key ingredient in the incremental risk associated with MDD relapse, alone or in combination with other variables (mood reactivity) such as rumination. However, future research should attempt to integrate and investigate, in a broader fashion with in-depth focus, the factors that impact relapse in MDD. Aside from cognitive, demographic (eg, gender), and neuropathological factors, there is an abundance of environmental factors that have been shown to be associated with increased risk for MDD relapse, not to mention other potentially mediating factors. Inflammatory mechanisms represent such a set of potentially mediating factors, particularly polymorphisms, which may be able to mediate genetic with environmental variables associated with increased risk for MDD relapse. Understanding the complex intercurrent relationship(s) among all of these variables and their independent and synergistic effects has the potential to assist the development of preventative interventions and treatments using various approaches to mitigate the effects and reduce the rates of MDD relapse.

Submitted: December 18, 2014; accepted December 23, 2014.

Potential conflicts of interest: The author reports no conflict of interest associated with this work.

Funding/support: The author did not receive funding for this work.

REFERENCES

1. Major Depression Among Adults. National Institute of Mental Health Web site. http://www.nimh.nih.gov/health/statistics/prevalence/major-depression-among-adults.shtml Accessed June 24, 2015.
2. US YLDs Contributed by Mental and Behavioral Disorders. National Institute of Mental Health Web site. http://www.nimh.nih.gov/health/statistics/disability/us-ylds-contributed-by-mental-and-behavioral-disorders.shtml.
3. Figueroa CA, Ruhé HG, Koeter MW, et al. Cognitive reactivity versus dysfunctional cognitions and the prediction of relapse in recurrent major depressive episode. *J Clin Psychiatry*.2015;76(10):e1306–e1312.
4. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition. Washington, DC: American Psychiatric Association; 2013:165.
5. Mueller TI, Leon AC, Keller MB, et al. Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. *Am J Psychiatry*. 1999;156(7):1000–1006.
6. Wisner KL, Perel JM, Peindl KS, et al. Prevention of postpartum depression: a pilot randomized clinical trial. *Am J Psychiatry*. 2004;161(7):1290–1292.
7. Llorente AM, Jensen CL, Voigt RG, et al. Effect of maternal docosahexaenoic acid supplementation on postpartum depression and information processing. *Am J Obstet Gynecol*. 2003;188(5):1348–1353.
8. Nolen-Hoeksema S, Morrow J. A prospective study of depression and posttraumatic stress symptoms after a natural disaster: the 1989 Loma Prieta Earthquake. *J Pers Soc Psychol*. 1991;61(1):115–121.
9. van Rijsbergen GD, Bockting CL, Burger H, et al. Mood reactivity rather than cognitive reactivity is predictive of depressive relapse: a randomized study with 5.5-year follow-up. *J Consult Clin Psychol*. 2013;81(3):508–517.
10. Beck AT. *Depression: Clinical, Experimental, and Theoretical Aspects*. New York, NY: Harper and Row; 1967.
11. Schildkraut JJ. The catecholamine hypothesis of affective disorders: a review of supporting evidence. *Am J Psychiatry*. 1965;122(5):509–522.
12. Teasdale JD. Cognitive vulnerability to persistent depression. *Cogn Emotion*. 1988;2(3):247–274.
13. Farb NA, Anderson AK, Bloch RT, et al. Mood-linked responses in medial prefrontal cortex predict relapse in patients with recurrent unipolar depression. *Biol Psychiatry*. 2011;70(4):366–372.
14. Gotlib IH, Hamilton JP. Neuroimaging and depression: current status and unresolved issues. *Curr Dir Psychol Sci*. 2008;17:159–163
15. Felger JC, Lotrich FE. Inflammatory cytokines in depression: neurobiological mechanisms and therapeutic implications. *Neuroscience*. 2013;246:199–229.
16. Maes M. Evidence for an immune response in major depression: a review and hypothesis. *Prog Neuropsychopharmacol Biol Psychiatry*. 1995;19(1):11–38.
17. Maes M, Berk M, Goehler L, et al. Depression and sickness behavior are Janus-faced responses to shared inflammatory pathways. *BMC Med*. 2012;10(1):66.
18. Moylan S, Maes M, Wray NR, et al. The neuroprogressive nature of major depressive disorder: pathways to disease evolution and resistance, and therapeutic implications. *Mol Psychiatry*. 2013;18(5):595–606.
19. Leonard B, Maes M. Mechanistic explanations how cell-mediated immune activation, inflammation and oxidative and nitrosative stress pathways and their sequels and concomitants play a role in the pathophysiology of unipolar depression. *Neurosci Biobehav Rev*. 2012;36(2):764–785.
20. Möller M, Du Preez JL, Viljoen FP, et al. Social isolation rearing induces mitochondrial, immunological, neurochemical and behavioural deficits in rats, and is reversed by clozapine or N-acetyl cysteine. *Brain Behav Immun*. 2013;30:156–167.