Illness comorbidity as a biomarker?

Hymie Anisman, PhD; Shawn Hayley, PhD

Department of Neuroscience, Carleton University, Ottawa, Ont.

Physical illnesses can be markers for subsequent psychological disturbances, and conversely, mental health problems can be markers of later physical pathologies. More importantly, the presence of one condition can limit treatment efficacy with respect to other pathological conditions. In this regard, illnesses frequently do not appear in isolation of one another, and more often than not, one or more additional illnesses may be associated with the primary disease or disorder. These comorbid disorders might coexist independently; one condition might arise as a result of the other, or one condition might be associated with a predisposition to the second without being causally related to it.[1] Comorbidity is exceptionally common with regard to physical illnesses; diabetes, like obesity, is often predictive of heart disease. Likewise, physical illnesses, such as heart disease and multiple sclerosis (MS), are associated with subsequent depressive disorder. Conversely, psychiatric illnesses, such as depression and schizophrenia, are comorbid with numerous immunological disorders, addiction, neurodegenerative disorders, metabolic syndrome and obesity.[2,3]

Psychiatric comorbidities can come about through several processes. An illness, such as heart disease or MS, may promote depression as individuals find their lifestyle being altered or because of the existential threat imposed. Conversely, depression, which is a fairly severe stressor, places considerable strain on an individual, culminating in inflammatory immune dysregulation that exacerbates MS symptoms and may influence the course of heart disease. It would be understandable to find depressive symptoms manifested after an MS or Parkinson disease diagnosis;[4] however, depressive disorders often precede diagnoses of these illnesses,[5,6] and depression in patients is more common than would ordinarily be expected in illnesses of a chronic nature.[4]

Comorbidity can also occur because an illness might give rise to neuroendocrine, neurotransmitter or cytokine changes that lead to a second disorder (e.g., among obese individuals, adipokines released from adipose tissue might promote depression) or because several disorders might have common underlying mechanisms. For instance, elevated cytokines may be a common denominator linking depression to cardiovascular disease, diabetes, Parkinson disease and, in some instances, cancer.[2,7] The fact that these illnesses have some common mechanisms associated with them does not necessarily imply that the etiological pathway(s) leading to these common features are the same. For example, altered levels of brain inflammatory factors could come about as a result of systemic infection or as a result of stressor experiences, but both might culminate in major depressive disorder. Similarly, in addition to the disturbances of dopamine neurons in the substantia nigra responsible for motor symptoms of Parkinson disease, serotonergic and noradrenergic neurons degenerate to a considerable degree,[8] which might contribute to depression. It is sometimes the case that a single etiological factor could cause 2 very different outcomes (e.g., smoking causes gum disease and heart disease), but these comorbid conditions might be entirely independent of one another.

The nature of the comorbid conditions expressed may have important clinical ramifications and fundamental implications regarding research focused on defining the processes that lead to disease and on the development of potential treatments. From the clinical side, when comorbid conditions are identified, decisions need to be made so that treatment of one illness does not aggravate the other. Likewise, the extent to which focus is placed on the secondary condition must be considered. For instance, it has been reported that anxiety and depression were accompanied by a poorer response to neoadjuvant chemotherapy for breast cancer (administration of therapeutic agents before initiating the primary treatment, e.g., hormone treatment administered before radical treatments).[9] Likewise, it has been reported that stroke is frequently followed by depressive illness and that the presence of depression signals a poor prognosis for recovery from stroke.[10] Interestingly, the same genes that often have been associated with major depression (e.g., short alleles for the serotonin transporter, 5-HTT, and the val66met brain-derived neurotrophic factor [BDNF] polymorphism) have also been associated with the occurrence of post-stroke depression.[11] In addition, following stroke, inflammation (reflected by elevated cytokine levels) is exceptionally high in the brain, and it has been suggested that intervention to deal with inflammation might enhance stroke recovery.[12] Essentially, to realize

more efficient treatment outcomes for stroke patients, particular attention ought to be devoted to dealing with the comorbid depression or its underlying processes as well as the chronic distress that accompanies stroke, which may place excessive strain (allostatic overload) on adaptive biological coping systems.[13]

In recent years there have been calls for 2 interlinked lines of research: one to define the biomarkers that are predictive of illness development or recurrence and one for the identification of appropriate individualized treatment strategies. The identification of biomarkers holds promise for predicting later pathologies and for tailoring individualized treatments. In this regard, it is likely that specific biological patterns or "signatures" that characterize a particular comorbid state will be more informative than consideration of specific individual markers in isolation of one another. It has been suggested that inflammatory cytokine signatures can be used to determine the likelihood that patients with Parkinson disease might experience comorbid depression,[14] just as responses to a combined dexamethasone/corticotropin-releasing hormone challenge might predict later responses to antidepressant medication.[15] In some instances, as in the case of cytokines, biological substrates may be highly pleiotropic, redundant in many of their actions, and disease nonspecific (associated with several immune and circulatory conditions). Yet, by assessing multianalyte disease profiles, altered cytokine levels might be useful as an adjunctive tool or "add-on" for clinical diagnostics.

Biomarkers can be indicative of more than just illness vulnerability, as they can also point to the efficacy of particular treatment strategies and might also predict illness recurrence. In particular, just as depression influences the course of recovery from other illnesses, it is equally possible that the presence of substrates associated with some pathological conditions might limit the effectiveness of treatments that would otherwise attenuate depressive illness. In fact, in animals, inflammation provoked through administration of a bacterial endotoxin reduced the antidepressant efficacy of fluoxetine,[16] and in humans, higher levels of inflammatory markers, particularly proinflammatory cytokines, were more apt to be associated with treatment resistance in response to selective serotonin reuptake inhibitors (SSRIs).[17]

Besides inflammatory processes, substantial attention has been devoted to the possibility that disturbed neuroplasticity contributes to the development of depression. Reduced hippocampal volume in patients with depression has been reported,[18] and animal studies indicated reduced neurogenesis and morphological abnormalities in stressor-based models of the disorder.[19] In its capacity to influence neuronal growth, BDNF has been identified as a potentially important substrate in relation to depressive illness,[20] as have other growth factors. Several studies have also suggested that changes in peripheral BDNF levels are reflective of brain concentrations of this trophic factor and, hence, might hold particular utility as a biomarker.[21] A major caveat to this, however, is that BDNF (like cytokines) is not disease specific, having been implicated in numerous pathologies of central or peripheral origin.[22] Thus, once again, multianalyte profiling would be a useful approach wherein BDNF would be one factor (albeit one with potentially considerable weight) contributing to some overall chemical signature.

Consideration of biomarkers leads into the topical issue of individualized treatments. One could use biomarkers as a screen to guide how specific individual treatments could be designed. This approach is reinforced by the perspective that drug treatments have not been overwhelmingly successful (e.g., in the case of antidepressants), and some clinicians/researchers have maintained that the effectiveness of SSRIs and serotonin–norepinephrine reuptake inhibitors are only a touch better than placebo. Of course, this often voiced critique ought to be a bit muted given that the odds of improvement are much better when a multitargeted approach is used, as opposed to using single compounds as in most drug trials.[23]

The less than stellar effectiveness of specific pharmacotherapy is not unique to treatments of mental disorders. In general, analgesics have a positive effect in 80% or more of patients; treatment efficacy for asthma and arrhythmia is about 60%; for diabetes, migraine and rheumatism it is 50%; for osteoporosis, hepatitis C and urinary incontinence it is 40%–50%; and for cancer it is down at about 25%.[24] Thus, for these disorders, as in the case of mental illness, there has been an increasing desire to identify the most effective treatment strategies based on individual characteristics. In this regard, an eminently reasonable tack would be one that entails an endophenotype-like approach in which specific illness symptoms (or clusters) would be tied to particular genetic factors, and these in turn, would be aligned with the most efficacious treatments.[25]

Strictly speaking, an endophenotype is state-independent and thus should be apparent irrespective of whether the illness is currently present. That said, it would not be surprising to find that certain biomarkers would be most apparent when an individual's system is under challenge (e.g., the extent of a biological change or the time for normalization of these outcomes), much like indices of cardiovascular problems are more apparent using a stress test than under resting conditions. Thus, the presence of particular markers (as well as symptoms or clusters of symptoms) might have implications for the subsequent development of illness and for the treatments that might be most efficacious. Likewise, given the frequency of comorbid illnesses and the possibility that they have common underlying features, the inclusion of illness might be useful as a biomarker for the evolution of other conditions. Essentially, illnesses, such as heart disease or certain immune-related disorders, particularly if accompanied by inflammatory changes, might be predictive of subsequent psychopathology and could potentially presage the treatment strategies that would be most efficacious.

References

1. Valderas JM, Starfield B, Sibbald B, et al. Defining comorbidity: implications for understanding health and health services. *Ann Fam Med* 2009;7:357-63.
2. Anisman H, Merali Z, Hayley S. Neurotransmitter, peptide and cytokine processes in relation to depressive disorder: comorbidity

between depression and neurodegenerative disorders. *Prog Neurobiol* 2008;85:1-74.

3. Mitchell AJ, Vancampfort D, Sweers K, et al. Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders — a systematic review and meta-analysis. *Schizophr Bull* 2012 Dec 29. [Epub ahead of print]

4. Patten SB, Beck CA, Williams JV, et al. Major depression in multiple sclerosis: a population-based perspective. *Neurology* 2003;61:1524-7.

5. Scott TF, Allen D, Price TR, et al. Characterization of major depression symptoms in multiple sclerosis patients. *J Neuropsychiatry Clin Neurosci* 1996;8:318-23.

6. McDonald WM, Richard IH, DeLong MR. Prevalence, etiology, and treatment of depression in Parkinson's disease. *Biol Psychiatry* 2003;54:363-75.

7. Ridker PM. Inflammatory biomarkers and risks of myocardial infarction, stroke, diabetes, and total mortality: implications for longevity. *Nutr Rev* 2007;65:S253-9.

8. Jellinger KA. Pathology of Parkinson's disease. Changes other than the nigrostriatal pathway. *Mol Chem Neuropathol* 1991;14:153-97.

9. Chintamani, Gogne A, Khandelwal R, et al. The correlation of anxiety and depression levels with response to neoadjuvant chemotherapy in patients with breast cancer. *JRSM Short Rep* 2011;2:15.

10. Bilge C, Koçer E, Koçer A, et al. Depression and functional outcome after stroke: the effect of antidepressant therapy on functional recovery. *Eur J Phys Rehabil Med* 2008;44:13-8.

11. Kim JM, Stewart R, Bae KY, et al. Serotonergic and BDNF genes and risk of depression after stroke. *J Affect Disord* 2012;136:833-40.

12. Langdon KD, Maclellan CL, Corbett D. Prolonged, 24-h delayed peripheral inflammation increases short- and long-term functional impairment and histopathological damage after focal ischemia in the rat. *J Cereb Blood Flow Metab* 2010;30:1450-9.

13. 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;1032:1-7.

14. Litteljohn D, Hayley S. Cytokines as potential biomarkers for Parkinson's disease: a multiplex approach. In: Yan Q, editor. *Psychoneuroimmunology: methods and protocols*. New York (NY): Springer Science, Humana Press; 2012.

15. Ising M, Horstmann S, Kloiber S, et al. Combined dexamethasone/corticotropin releasing hormone test predicts treatment response in major depression — A potential biomarker? *Biol Psychiatry* 2007;62:47-54.

16. Wang Y, Cui XL, Liu YF, et al. LPS inhibits the effects of fluoxetine on depression-like behavior and hippocampal neurogenesis in rats. *Prog Neuropsychopharmacol Biol Psychiatry* 2011;35:1831-5.

17. O'Brien SM, Scully P, Fitzgerald P, et al. Plasma cytokine profiles in depressed patients who fail to respond to selective serotonin reuptake inhibitor therapy. *J Psychiatr Res* 2007;41:326-31.

18. Sheline YI, Gado MH, Kraemer HC. Untreated depression and hippocampal volume loss. *Am J Psychiatry* 2003;160:1516-8.

19. Schmidt HD, Duman RS. The role of neurotrophic factors in adult hippocampal neurogenesis, antidepressant treatments and animal models of depressive-like behavior. *Behav Pharmacol* 2007;18:391-418.

20. Duman RS, Monteggia LM. A neurotrophic model for stress-related mood disorders. *Biol Psychiatry* 2006;59:1116-27.

21. Klein AB, Williamson R, Santini MA, et al. Bood BDNF concentrations reflect brain-tissue BDNF levels across species. *Int J Neuropsychopharmacol* 2011;14:347-53.

22. Autry AE, Monteggia LM. Brain-derived neurotrophic factor and neuropsychiatric disorders. *Pharmacol Rev* 2012;64:238-58.

23. Blier P, Ward HE, Tremblay P, et al. Combination of antidepressant medications from treatment initiation for major depressive disorder: a double-blind randomized study. *Am J Psychiatry* 2010;167:1281-8.

24. RIKEN. Advancing personalized medicine: tailoring drugs to fit a patient's genetic predisposition. *Science Daily* (2012 Feb. 25). Available: www.sciencedaily.com/releases/2012/02/120224152755.htm (accessed 2012 May 15).

25. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry* 2003;160:636-45.

*Based on page views on PubMed Central of research, reviews and commentaries published in the last 5 years.