Published in final edited form as:

J Am Acad Child Adolesc Psychiatry. 2014 July ; 53(7): 720–722. doi:10.1016/j.jaac.2014.03.010.

Inflammatory Depressive Bowel Diseases – the new era

Eyal Shemesh, M.D. and Vilma Gabbay, M.D.

Department of Pediatrics and the Kravis Children's Hospital (ES), the Department of Psychiatry (ES, VG), Icahn School of Medicine at Mount Sinai, New York, and the Nathan Kline Institute for Psychiatric Research (VG) New York.

In this issue, xxx et al. (1) describe a prospective randomized controlled trial that evaluated two different non-pharmacological therapies [cognitive-behavioral therapy (CBT) versus supportive care], delivered to depressed children and adolescents with inflammatory bowel disease (IBD). Other prospective, randomized trials of treatments for depression in medically-ill individuals showed that Sertraline is no better than placebo in patients with heart failure (2), that CBT does not improve medical outcomes after a myocardial infarction, and that both psychotherapy and usual care are associated with improved depressive symptoms in that setting (3). Consistent with those other studies, xxx et al observed no significant differences in post-intervention depressive symptom severity between the two approaches. The authors conclude that both treatments were very effective, based on a reduction in depression severity scores in both groups. This might be the case, but since the study did not have an attention control, we do not know for sure whether any of those treatments is superior to simply paying careful attention to patients. A reasonable conclusion from the study, we think, is that “no matter what the Doctor does, as long as the patient receives personal attention, it will work” in reducing depressive symptoms.

Thus, the present study joins other rigorous studies which, together, report that Sertraline, Placebo, cognitive-behavioral therapy, and supportive therapy are all quite effective in alleviating depression in physically-ill individuals, while none is clearly superior to any other. It is time, in our view, for a pause. Rather than continue looking for one specific treatment that would be significantly better than any others in physically ill patients who are also depressed (or suffer from any other comorbid psychiatric disorder), one should recognize that many treatments would probably work just fine in this setting. The inconvenient truth is that patients seen in medical care settings are under-treated for depression (4) as well as other mental health disorders. In a situation in which almost anything will help our patients, we typically offer.. nothing. This, clearly, needs to change.

Physically-ill individuals with comorbid depression are a particularly complex group of patients. Depression is defined as a cluster of symptoms in addition to severe sadness or anhedonia. The diagnostic criteria, which are not very specific to begin with, can be due to biological (genetic and other) predisposition, social circumstances, or interpersonal problems, to name just a few. To this blurry mix, the addition of a chronic physical illness (with its own set of genetic predispositions or correlates, other biological correlates, disabling features, social implications, distress about prognosis, interpersonal effects, and so on), results in a complex amalgam of biology and circumstances which may well be quite unique for each individual. Clearly, if anyone could show that one specific treatment is “the

best”, there would be important clinical benefits (streamlining of therapy) as well as perhaps significant financial advantages (to the developer of the treatment or patent-holders). But this has not happened yet, and we should perhaps conclude that different modalities may help different people, whereas putting everyone together and studying one specific modality makes little sense. A varied and nuanced strategy emerges as the only evidence-based approach, since no single modality can be said to have the kind of evidence that would promote its use over all others.

So where do we go from here? – the first step, we propose, is to concentrate on safety studies. If any single modality is no better than the other, safety could become the most important factor in choosing a treatment, and yet very few studies attempted to look at the safety of medications or psychotherapy in physically-ill individuals. As we previously argued (5), there is no reason to give psychotherapies a “free pass” when it comes to safety, and yet we are aware of only one rigorous medical safety study of a specific psychotherapy in medically-ill patients (5).

The second step is to try to investigate the effects of specific treatments on specific symptom clusters, while attempting to understand the biological or behavioral mechanisms that are in play, so that one can target therapeutic efforts to a particular mechanism if it exists. The manuscript by xxxx provides clues to the exciting and interesting path ahead.

Specific mechanisms within the more general constellation of symptoms that constitute a mental health disorder may interact in a unique way with physical illness to produce devastating outcomes. For example, the avoidance cluster of posttraumatic stress disorder is associated with nonadherence to medical recommendations, perpetuating a “vicious cycle” in which the patient tries to avoid reminders of the illness, therefore does not take the medications (which serve as a reminder), becomes sicker and therefore more distressed and avoidant, and so on (6). “Zooming in” on this particular pathway may be a cost-effective way to target the few patients who drive many of the poor outcomes.

XXX et al. imply that there might be merits to a more individualized approach when they review their finding that CBT might have led to more substantial improvement in IBD medical outcomes (although as a secondary measure, this result will have to be replicated if it is to be considered further). The high prevalence of depression among physically ill patients hints that overlapping biological mechanisms may underlie both the physical and psychiatric illnesses. Indeed, as xxx hint in their article, activation of the peripheral immune system—relevant to many physical disorders including IBD—was shown to play a role in depression (7). The specific mechanisms seem to involve disturbances in the reward circuitry, manifested clinically as anhedonia, which is a reduced capacity to experience pleasure (and a hallmark of depression). It has been argued that such responses reflect motivational reorganization in order to conserve energy needed to facilitate the healing process. Findings include decreased striatal activation to rewarding stimuli subsequent to administration of immunological stimulator (interferon or endotoxin) to healthy and physically ill individuals (8). As such, the clinical manifestation of anhedonia (or depression) among some youth with IBD may be an additional symptom of the inflammatory illness. Clinically, recent work has shown that anhedonia assessed both

categorically (present or not) and quantitatively among depressed individuals is associated with inflammatory markers (9) in the blood and CNS. In parallel, among patients with heart disease, anhedonia (but not depressed mood) was identified as a predictor for major adverse cardiac events at 1 year post admission (10). Taken together, these findings suggest that treatments that target specific symptoms (such as anhedonia) in the context of a physical illness may alleviate both the physical and the psychiatric manifestation related to the same inflammatory mechanisms.

“Personalized medicine” has been successful in some circumstances (i.e., in cancer treatments). In our view, the next generation of mental health treatment studies must actively engage in this approach, beginning with the basics - finding markers that “flag” individual patients who might benefit from one approach or another. It is time to stop asking which approach works better than others in general. The important study by xxxx et al. should usher us into a new era in which the questions are, what are the mechanisms that lead to poor outcomes, how can we alter those processes, when should we intervene and with whom, and which intervention fits which circumstances the best.

Acknowledgments

Eyal Shemesh would like to acknowledge the support of NIDDK grant # R01DK08740 (Shemesh, PI).

Vilma Gabbay would like to acknowledge the support of NIMH grant # MH095807 (Gabbay, PI).

References

1. NEW ARTICLE FULL REFERENCE HERE.
2. O'Connor CM, Jiang W, Kuchibhatla M, Silva SG, Cuffe MS, Callwood DD, Zakhary B, Stough WG, Arias RM, Rivelli SK, Krishnan R. SADHART-CHF Investigators. Safety and efficacy of sertraline for depression in patients with heart failure: results of the SADHART-CHF (Sertraline Against Depression and Heart Disease in Chronic Heart Failure) trial. *J Am Coll Cardiol*. 2010 Aug 24; 56(9):692–699. [PubMed: 20723799]
3. Berkman LF, Blumenthal J, Burg M, Carney RM, Catellier D, Cowan MJ, Czajkowski SM, DeBusk R, Hosking J, Jaffe A, Kaufmann PG, Mitchell P, Norman J, Powell LH, Raczynski JM, Schneiderman N. Enhancing Recovery in Coronary Heart Disease Patients Investigators (ENRICH). Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICH) Randomized Trial. *JAMA*. 2003 Jun 18; 289(23):3106–3116. [PubMed: 12813116]
4. Sederer, LI.; Petit, JR.; Paone, D.; Ramos, S.; Ribin, J.; Christman, M. Joint Center For Political And Economic Studies, Health Policy Institute. Washington, D.C.: Web document; Changing the landscape: depression screening and management in primary care. [accessed 3/21/2014]
5. Shemesh E, Annunziato RA, Weatherley BD, Cotter G, Feaganes JR, Santra M, Yehuda R, Rubinstein D. A randomized controlled trial of the safety and promise of cognitive-behavioral therapy using imaginal exposure in patients with posttraumatic stress disorder resulting from cardiovascular illness. *J Clin Psychiatry*. 2011 Feb; 72(2):168–174. [PubMed: 20441725]
6. Cotter G, Milo-Cotter O, Rubinstein D, Shemesh E. Posttraumatic stress disorder: a missed link between psychiatric and cardiovascular morbidity? *CNS Spectr*. 2006 Feb; 11(2):129–136. [PubMed: 16520690]
7. Zunszain PA1, Hepgul N, Pariante CM. Inflammation and depression. *Curr Top Behav Neurosci*. 2013; 14:135–151. [PubMed: 22553073]
8. Capuron L, et al. Dopaminergic mechanisms of reduced basal ganglia responses to hedonic reward during interferon alfa administration. *Archives of general psychiatry*. 2011; 69:1044–1053. [PubMed: 23026954]

9. Gabbay V, Ely BA, Babb J, Liebes L. The possible role of the kynurenine pathway in anhedonia in adolescents. *J Neural Transm.* 2012; 119:253–260. [PubMed: 21786117]
10. Davidson KW, et al. Association of anhedonia with recurrent major adverse cardiac events and mortality 1 year after acute coronary syndrome. *Archives of general psychiatry.* 2010; 67:480–488. [PubMed: 20439829]