Letters to the editor

DRUG ALLERGIES AND CHILDHOOD TRAUMA AMONG CHRONIC PAIN PATIENTS

DEAR EDITOR:

Trauma appears to be a specific psychosocial variable that potentially heightens an individual's emotional response to the external environment. Although not everyone develops this syndrome in the aftermath of childhood trauma, perhaps the best example of this phenomenon is posttraumatic stress disorder (PTSD) and the subsequent clinical finding of hyperarousal.[1] Another example might be multiple chemical sensitivities (MCS), a controversial syndrome in which individuals experience adverse physical reactions to low levels of common chemicals.[2] Magill and Suruda[3] state that, "there are marked similarities between MCS and posttraumatic stress disorder." In an effort to expand upon this trauma/hypersensitivity paradigm, we hypothesized that medications may represent an environmental element and that there might be a relationship between histories of childhood trauma (e.g., sexual, physical, and/or emotional abuses; witnessing violence; and physical neglect) and the number of patient-reported drug allergies. Indeed, in an earlier study, we determined that outpatients with borderline personality disorder, in which trauma is a contributory substrate, evidenced a marginal statistically significant relationship with the number of self-reported drug allergies.[4] However, in this latter study, we did not explore histories of trauma.

In the present study, participants consisted of 117 chronic noncancer pain patients (response rate: 94.4%; 43 men, 73 women) who were referred to a pain-management specialist by physicians predominantly in the areas of physical medicine and rehabilitation, orthopedics, and primary care. All participants were insured, and in this practice setting, 37 percent of patients are covered through workers compensation and 63 percent through private insurance (i.e., no Medicare or Medicaid sponsorship). We elected to examine this population because of the anticipated high frequency of childhood trauma. The sample ranged in age from 18 to 69 years (M=44.50, SD=11.50). With regard to race/ethnicity, 105 (89.7%) participants were Caucasian, six (5.7%) were Hispanic, three (2.6%) were African-American, one (0.8%) was Asian, and two (1.7%) were "other." Sixty of the subjects were married (51.3%), 26 (22.2%) were never married, 26 (22.2%) were divorced, four (3.4%) were separated, and one (0.8%) was widowed. Nine (7.7%) did not graduate high school, 25 (21.4%) graduated high school only, 39 (33.3%) attended some college, 27 (23.1%) had college degrees, and 17 (14.5%) had graduate degrees.

Participants were recruited during their initial clinical evaluations for chronic pain. Each completed a research booklet that explored personal demographics, drug allergies (write-in section), and histories of childhood trauma. The definition of "drug allergy" was not provided. With regard to childhood trauma, participants were asked, "Prior to the age of 12, did you ever experience…" with yes/no response options regarding the following: sexual abuse ("any sexual activity against your will"); physical abuse ("any physical insult against you that would be considered inappropriate by either yourself or others and that left visible signs of damage on your body either temporarily or permanently or caused pain that persisted beyond the 'punishment'"); emotional abuse ("verbal and nonverbal behaviors by another individual that were purposefully intended to hurt and control you, not kid or tease you"); physical neglect ("not having your basic life needs met"); and witnessing of violence ("the first-hand observation of violence that did not directly involve you"). Beyond face validity, this brief trauma assessment had no determined validity or reliability. We elected the preceding brief inquiry for childhood trauma because of our concerns about the possible negative impact of longer and more detailed surveys among chronic pain patients being seen in a busy clinic setting. The project was approved by an institutional review board and completion of the research booklet was assumed to function as informed consent (i.e., the first page of the booklet clearly stated that the results of this anonymous survey would be used in a study by the authors).

As for results, 33 (28.2%) participants reported having experienced sexual abuse, 35 (29.9%) physical abuse, 58 (49.6%) emotional abuse, 12 (10.3%) physical neglect, and 45 (38.5%) the witnessing of violence. Only 45 (38.5%) denied having experienced any of the five forms of trauma. Most (61; 52.1%) reported having experienced one, two, or three different types of childhood trauma.

All participants reported between 0 and 4 allergies to individual medications, with the exception of one participant who reported eight allergies. (To prevent this unusual outlier from exerting too much statistical influence, this patient's number of allergies was recoded to 4.) Specifically, 74 participants

reported no allergies, 25 one allergy, 12 two, 3 three, and 3 four. The overwhelming majority of allergies were attributed to antibiotics and analgesics. In the resulting analyses, the total number of allergies was positively correlated with the total number of different traumas indicated (r=0.19, $p<0.05$). In examining the specific types of childhood trauma, the total number of allergies statistically differed between the trauma and no-trauma groups for both witnessing violence and sexual abuse. Specifically, those who witnessed violence in childhood reported more allergies (M=0.84, SD=1.09) compared to those who did not witness violence ([M=0.44, SD=0.84], t[1,115]=-2.24, $p<0.03$). Similarly, those who experienced sexual abuse in childhood reported more allergies (M=0.91, SD=1.16) compared to those who did not experience sexual abuse ([M=0.48, SD=0.84], t[1,115]=-2.24, p<0.03.)

These data highlight a possible relationship between trauma and environmental sensitivity in the form of allergies to medications. We do not know if these reported allergies are genuine, exaggerated, adverse medication effects, or factitious. However, that specific environmental substances are less tolerated in traumatized patients tends to reinforce the trauma/hypersensitivity paradigm observed in PTSD and MCS. If these findings are valid, then patients with multiple allergies to medications may be more likely to have histories of trauma with secondary sensitivity or reactivity to the environment in the form of drug allergies—an important finding for both psychiatrists and primary care physicians. In other words, multiple allergies may be a nonspecific clinical indicator of the possible presence of childhood trauma, and thereby alert clinicians to examine the patient's history for evidence. In addition, such histories may culminate in a number of potential psychiatric and medical syndromes.

The potential limitations of this study include the small sample size, self-report nature of the data, the absence of a definition for "drug allergies" (i.e., a heightened risk of false positives), and the lack of a standardized assessment of childhood trauma. However, this is the first study to our knowledge to explore medication allergies and their specific relationship to childhood trauma in an outpatient, chronic-pain population. Our findings lend support to a trauma/hypersensitivity paradigm.

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Press, Inc., 1994.
2. US Department of Labor Occupational Safety and Health Administration. Multiple chemical sensitivities. 2008. http://www.osha.gov/SLTC/multiplechemicalsensitivies/index/html. Accessed on November 25, 2008.
3. Magill MK, Suruda A. Multiple chemical sensitivity syndrome. http://www.aafp.org/afp/980901ap/magill.html. Accessed on November 25, 2008.
4. Sansone RA, Gentile J, Markert RJ. Drug allergies among patients with borderline personality symptomatology. *Gen Hosp Psychiatry.* 2000;22:289–293.

With regards,

Randy A. Sansone, MD
Professor, Psychiatry and Internal Medicine, Wright State University School of Medicine, Dayton, Ohio; Director, Psychiatry Education, Kettering Medical Center, Kettering, Ohio

J. David Sinclair, MD, FRCP
private practice, independent consultant for management of chronic non-cancer pain, Seattle, Washington

Michael W. Wiederman, PhD
Professor of Psychology, Department of Human Relations, Columbia College, Columbia, South Carolina

ADDRESS CORRESPONDENCE TO:
Randy A. Sansone, MD, Sycamore Primary Care Center, 2115 Leiter Road, Miamisburg, OH 45342. Phone: (937) 384-6850; Fax: (937) 384-6938; E-mail: Randy.sansone@khnetwork.org

DEPRESSION AND CORONARY ARTERY DISEASE

DEAR EDITOR:

In the January 2009 issue of *Psychiatry* (Edgemont), Khawaja et al[1] provided a masterful and exhaustive elucidation of the bidirectional association between depression and coronary artery disease. The pathways from depression to coronary artery disease are complex and circuitous. They include autonomic dysfunction, hypothalamic-pituitary adrenal axis hyperactivity, platelet activation, and release of proinflammatory cytokines. An emerging body of literature implicates coronary risk factors, such as hypertension, diabetes, dyslipidemia, cigarette smoking, and obesity, in the pathogenesis of "vascular" depression.[2] The vascular depression hypothesis initially emerged with the discovery that depression with an onset in late life is commonly associated with subcortical and periventricular brain white matter hyperintensity (WMH) microvascular lesions, visualized on magnetic resonance imaging.[2] A recent longitudinal study of 639 older patients conducted in 11 European centers revealed a correlation between the intensity of WMH lesions and the subsequent development of depression.[3] These subcortical brain lesions appear to interrupt the integrity of vital frontostriatal limbic circuits providing a biological

substrate for vascular depression. This is a condition distinguished by apathy, executive function deficits, and resistance to antidepressant treatment.[4] At least one promising study has suggested that lowering blood pressure reduces the progression of WMH lesions.[4] Managing hypertension is known to reduce the risk of stroke. Similarly, lowering blood pressure may prevent late-life vascular depression.

Whereas the vascular depression hypothesis has focused exclusively on depression with an onset in late life, vascular risk factors may be equally relevant in the pathogenesis and course of depression in younger individuals.[5] We recently examined the influence of comorbid vascular factors on treatment outcome. Patients, ranging in age from 18 to 75 years, who were hospitalized with depression on the adult psychiatry unit of a general hospital in mid-Michigan completed a brief cardiovascular risk questionnaire. The cohort of patients referred for electroconvulsive therapy (ECT) following failure to respond to drug treatment was compared to that which responded to antidepressant medications. Forty-three (23%) of the 187 study patients who failed to respond to antidepressants were subsequently referred for ECT. These patients had a disproportionately high prevalence of cardiovascular risk factors. The relative risk of hypertension in drug nonresponders was 1.6, diabetes mellitus 2.4, dyslipidemia 1.8, and obesity 1.6. The presence of any cardiovascular risk factor was associated with a later onset of depression (Pearson correlation coefficient r=0.275, p=0.01). The SADHART and ENRICHD study, cited by Khawaja et al,[1] affirmed that in depression following myocardial infarction (MI), the use of selective serotonin reuptake inhibitor (SSRI) antidepressants is associated with a lower risk of subsequent MI recurrence and death. Is it possible that preventing hypertension, diabetes, and dyslipidemia will prevent depression in some susceptible individuals and improve the outcome of depression treatment in others?

REFERENCES

1. Khawaja IS, Westermeyer JJ, Gajwani P, Feinstein RE. Depression and coronary artery disease: the association, mechanisms, and therapeutic implications. *Psychiatry* (Edgemont). 2009;6(1):38–51.
2. Alexopoulos GS, Murphy CF, Gunning-Dixon FM, et al. Microstructural white matter abnormalities and remission of geriatric depression. *Am J Psychiatry.* 2008;165:238–244.
3. Teodorczuk A, O'Brien JT, Firbank MJ, Pet al. White matter changes and late-life depressive symptoms: Longitudinal study. *Br J Psychiatry.* 2007;191:212–217.
4. Schiffrin E. Blood pressure lowering in PROGRESS (Perindopril Protection Against Recurrent Stroke Study) and white matter hyperintensities: should this progress matter to patients? *Circulation.* 2005;112:1525–1526.
5. Iosifescu DV, Renshaw PF, Lyoo IK, et al. Brain white-matter hyperintensities and treatment outcome in major depressive disorder. *Br J Psychiatry.* 2006;188:180–185.

With regards,

Dale A. D'Mello, MD
Associate Professor, Department of Psychiatry, Michigan State University, East Lansing, Michigan

Alric Hawkins, MD
Resident, Department of Psychiatry, Vanderbilt University, Nashville, Tennessee

ADDRESS CORRESPONDENCE TO:
Dale A. D'Mello, MD, St. Lawrence/Sparrow Hospital, 1210 W. Saginaw, Lansing, MI 48915, Phone: (517)-364-7607, Fax (517)-364-7649, E-Mail: Dale.D'Mello@hc.msu.edu

AUTHOR RESPONSE

We appreciate the comments by D'Mello and Hawkins on our review article published in the January 2009 issue of *Psychiatry* (Edgemont).[1] They discuss an important issue of the effect of metabolic disorders on depression. One of the reasons why DSM IV removed the category of "organic depression" is that all psychiatric disorders have some "organic" basis to them.

D'Mello and Hawkins discuss the "vascular depression" hypothesis, referencing some studies that point to the relationship of subcortical and periventricular brain white matter hyperintensity (WMH) microvascular lesions as a cause of subsequent depression. The correlation of WMH and development of depression is an important and interesting finding. It is possible that microvascular disease causing these lesions could interrupt the integrity of the frontostriatal limbic circuits, thus making a person more susceptible to depression with distinguished clinical features, such as apathy, executive dysfunction, and treatment resistance to medications. We appreciate the authors sharing their study results, suggesting that the treatment-resistant group had more cardiovascular and metabolic comorbidities than those who are responders to medications. Does this damage cause cell death in certain areas of the brain? Increased neurogenesis in hippocampus has been hypothesized as a mechanism of electroconvulsive therapy (ECT),[2] and it would be interesting to see if the treatment-resistant group shows improvement in their depression with ECT.

We would like to add further to the discussion of metabolic disorder's effect on vascular health by pointing to the association of sleep disorders with cardiovascular health. In an 18-year follow up of the Wisconsin cohort study,[3] the adjusted hazard risk of

cardiovascular mortality of patients with untreated obstructive sleep apnea was 5.2 (1.4–19.2). Intermittent hypoxemia associated with sleep apnea has been linked to endothelial dysfunction causing direct damage to the vascular system.[4] In addition to this, in one study,[5] longer sleep duration was associated with reduced calcification incidence over five years. Pepperell et al[6] found a small but significant reduction in daytime blood pressure in a normotensive cohort after four weeks of continuous positive airway pressure (CPAP) therapy, especially for those who had frequent desaturation episodes. We wonder how many of D'Mello's treatment-resistant patients had sleep apnea.

We agree with the authors that it is plausible that preventing metabolic disorders or treating them effectively could prevent vascular depression. A large, prospective study should be conducted with the population at risk being treated aggressively for metabolic problems and compared to the controls of patients whose metabolic disorders are either uncontrolled or not treated. We encourage such a study to be conducted as it surely would further our understanding of the relationship between coronary artery disease, metabolic disorders, and depression.

REFERENCES

1. Khawaja IS, Westermeyer JJ, Gajwani P, Feinstein RE. Depression and coronary artery disease: the association, mechanisms, and therapeutic implications. *Psychiatry* (Edgemont). 2009;6(1):38–51.
2. Madsen TM, Treschow A, Bengzon J, et al. Increased neurogenesis in a model of electroconvulsive therapy. *Biol Psychiatry.* 2000;47:1043–1049.
3. Young T, Finn L, Peppard P, et al. Sleep disordered breathing and mortality: eighteen year follow-up of the Wisconsin sleep cohort. *Sleep.* 2008;31(8):1071–1078
4. Caples SM, Garcia-Touchard A, Somers VK. Sleep disordered breathing and cardiovascular risk. *Sleep.* 2007;30(3):291–303
5. King CR, Knutson KL, Tathouz PJ, et al. Short sleep duration and incident coronary artery calcification. *JAMA.* 2008;300(24):2859–2866.
6. Pepperell JC, Ramdassight-Dow S, Crosthwaite N, et al. Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomized parallel trial. *Lancet.* 2002;359:204–210.

With regards,

Imran S. Khawaja, MBBS
Psychiatrist, Sleep Medicine Physician, VA Medical Center Minneapolis, Minnesota; Assistant Professor, Department of Psychiatry, University of Minnesota; Fellow, Sleep Medicine, Mayo Clinic, Rochester, Minnesota

Joseph W. Westermeyer, MD, PhD
Professor of Psychiatry, Department of Psychiatry, University of Minnesota School of Medicine, Minneapolis, Minnesota; VA Medical Center, Minneapolis, Minnesota

Prashant Gajwani, MD
Hoffman-La Roche, Inc., Nutley, New Jersey

Robert E. Feinstein, MD
Professor of Psychiatry, Department of Psychiatry, University of Colorado, Denver, Colorado

ADDRESS CORRESPONDENCE TO:
Imran S. Khawaja, MBBS
One Veterans Dr., Minneapolis, MN 55417; E- mail: khimran@yahoo.com

LETTERS TO THE EDITOR SUBMISSIONS

Psychiatry 2009 welcomes submissions for possible publication in the Letters section. Letters should be no more than 500 words and five references. Type with double spacing. Letters that comment on a *Psychiatry 2009* article will be considered if they are received within two months of the time the article was published. All letters are reviewed by the editors and are selected based upon interest, timeliness, and pertinence, as determined by the editors. There are no guarantees a letter will be published. Letters that are not intended for publication by the authors should state this in the body of the letter. Published letters are edited and may be shortened; tables and figures are included only selectively.

Send letters to: Elizabeth Klumpp, Executive Editor, *Psychiatry 2009*, editorial@matrixmedcom.com. Hard copy submissions are no longer accepted.

Include the following statement with the letter: "The undersigned author transfers all copyright ownership of the enclosed/attached letter to Matrix Medical Communications in the event the work is published. The undersigned author warrants that the letter is original, is not under consideration by another journal, and has not been previously published. I sign for and accept responsibility for releasing this material on behalf of any and all co-authors."