Heart Rate Variability and Depression: Sleep-Related Breathing Disorders as Confounder?

Licht et al[1] discuss a relationship between depression and heart rate variability in their sample, which was also studied for the presence of other health-related variables, including heart disease and chronic medical conditions. Not specifically mentioned in their report is the presence of sleep-related breathing disorders (including sleep apnea) as a potential confounder, which is surprising given the evidence that exists linking these conditions to both diminished heart rate variability[2] and depression.[3]

The multiple overnight arousals that occur in sleep apnea result in a number of physiologic insults, including cardiac effects due to sympathetic activation as well as affective dysfunction related to nonrestorative sleep punctuated by apneic periods. Also, there are several diagnostic overlaps between the excessive daytime sleepiness that results from untreated sleep apnea and the symptoms of major depressive disorder, including mood alteration, diminished functionality, fatigue, sleep disturbance, and cognitive changes, all suggesting the possibility that an unaddressed sleep disorder may have had some bearing on covariance in this sample.

Subjects were evaluated for body mass index at the time of study, and while elevated body mass index values do correlate with the likelihood of obstructive sleep apnea being present, the syndrome does occur in individuals of normal weight.[4] While the presence of heart disease in subjects was acknowledged, the specific diagnoses mentioned (coronary disease, cardiac arrhythmia, angina pectoris, heart failure, and myocardial infarction) could themselves be conceptualized as sequelae of obstructive sleep apnea.

It is possible that sleep-related breathing disorders were addressed in the analysis; however, the absence of their mention in the publication leads the reader to ponder effects of this potential confounding variable.

Lara Kierlin, MD, MBA
Frisca Yan-Go, MD

Correspondence: Dr Kierlin, Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, 760 Westwood Plaza, Los Angeles, CA 90024 (lkierlin@mednet.ucla.edu).
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1. Licht CM, de Geus EJ, Zitman FG, Hoogendijk WJ, van Dyck R, Penninx BW. Association between major depressive disorder and heart rate variability in the Netherlands Study of Depression and Anxiety (NESDA). *Arch Gen Psychiatry*. 2008;65(12):1358-1367.
2. Narkiewicz K, Montano N, Cogliati C, van de Borne PJ, Dyken ME, Somers VK. Altered cardiovascular variability in obstructive sleep apnea. *Circulation*. 1998;98(11):1071-1077.
3. Bassiri AG, Guilleminault C. Clinical features and evaluation of obstructive sleep apnea–hypopnea syndrome. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 3rd ed. Philadelphia, PA: WB Saunders; 2000:869-878.
4. Lettieri CJ, Eliasson AE, Andrada T, Khramtsov A, Raphaelson M, Kristo DA. Obstructive sleep apnea syndrome: are we missing an at-risk population? *J Clin Sleep Med*. 2005;1(4):381-385.

Family-Focused Treatment for Adolescents With Bipolar Disorder

In the September 2008 issue of the *Archives*, Miklowitz and colleagues[1] present results of a 2-year randomized trial on family-focused treatment for adolescents with bipolar disorder (FFT-A). They conclude that FFT-A is effective in stabilizing bipolar depressive symptoms among adolescents.

Since this is the first published randomized psychotherapy trial in this population, the topic is of high importance and interest to colleagues from research and clinical practice. Unfortunately, however, the report lacks important information necessary to assess the actual efficacy of the intervention because Miklowitz and colleagues did not report the exact number of subjects per group who entered the study in a syndromally depressed state. On page 1057, they note that the rate of recovery from index-episode depressive symptoms was high in the FFT-A (30 of 30, 100%) and control (25 of 28, 89.3%) group but that the FFT-A group experienced more rapid recovery from initial depressive symptoms. However, these conclusions are misleading since, according to the sample description (page 1059), at least 21% of the total sample of 58 entered the study because of manic, not depressive, symptoms. Accordingly, recovery rates from initial depressive symptoms should correspond to the subgroups of patients who entered the study syndromally depressed and not to the total number of subjects per group. Furthermore, it cannot be ruled out that the different proportion of time spent without depressive symptoms during follow-up in the 2 samples (page 1058) was owing to a different proportion of patients who already entered the study without syndromal depression. Finally, Miklowitz and colleagues failed to report a significance test for the group difference in depression-free weeks for the subsample of patients entering the study in a syndromally depressed state (page 1058). Delineation of this information is important, particularly because of the overall small sample sizes in this study.

Christine Kuehner, PhD

Correspondence: Dr Kuehner, Research Group Longitudinal and Intervention Research, Department of Psychiatry and Psychotherapy, Central Institute of Mental Health, PO Box 122120, 68072 Mannheim, Germany (christine.kuehner@zi-mannheim.de).
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1. Miklowitz DJ, Axelson DA, Birmaher B, George EL, Taylor DO, Schneck CD, Beresford CA, Dickinson LM, Craighead WE, Brent DA. Family-focused treatment for adolescents with bipolar disorder: results of a 2-year randomized trial. *Arch Gen Psychiatry*. 2008;65(9):1053-1061.

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In reply

We appreciate Dr Kuehner's insightful comments. First, we calculated recovery from depression in all participants who showed significant depressive symptoms at intake, including patients who began in a syndromally depressed, mixed, or subsyndromally depressed state. Subsyndromal depressive symptoms were strongly associated with poor psychosocial functioning in a 2-year follow-up of children diagnosed with bipolar spectrum disorders.[1]

Table 1 in our article reports that, of the 58 adolescents, 18 (31.0%) met DSM-IV *criteria for a major depressive disorder at entry (>2 weeks in the past 3 months with Adolescent Longitudinal Interval Follow-up Evaluation*[2] *depression scores ≥5), and 25 (43.1%) met our research criteria for subsyndromal depression (1-2 weeks in the past 3 months with Adolescent Longitudinal Interval Follow-up Evaluation depression scores ≥3 [subthreshold] and <5). The 3 patients (5.2%) who entered in a mixed state also had concurrent major depression by these criteria. These illness designations were distributed equally across the FFT-A and enhanced care (EC) groups.*

Of the 12 patients (20.7%) who entered with mania, 5 also met our criteria for subsyndromal depression at entry. The 12 patients with mania were evenly divided between the FFT-A (n=6) and EC (n=6) groups; of the 7 without subsyndromal depression, 3 were allocated to FFT-A and 4 to EC. The effects of psychosocial treatment on time to recovery did not change (hazard ratio [HR], 2.15; P=.02*) when we excluded these 12 participants from the analysis. Thus, it seems unlikely that our results for depression recovery were due to a systematic bias in the random allocation of nondepressed bipolar participants to the treatment groups.*

Second, as noted in the article, there were no interactions between treatment group and baseline polarity or baseline clinical state in predicting time to recovery, depression-free weeks, time in depressive episodes, or the overall trajectory of depression symptoms over 2 years. The effect of psychosocial treatment on depression-free weeks was statistically significant (χ^2_1=8.14; P=.004*) in the subgroup of 21 patients who had a major depressive episode (n=18) or a mixed episode (n=3) at entry. The mean time to recovery from depression in the subset who had a major depressive episode was significantly shorter in the FFT-A than the EC subjects (15.3 vs 22.5 weeks; HR, 4.87;* P=.04*). Including the 3 additional subjects with a mixed episode yielded similar results (HR, 6.77;* P=.008*). The finding that syndromally depressed adolescents recovered 7.2 weeks earlier in FFT-A than in EC is clinically significant when considering the psychosocial costs of ongoing depression for adolescents and their families.*

David J. Miklowitz, PhD
David A. Axelson, MD
Boris Birmaher, MD
L. Miriam Dickinson, PhD

Correspondence: Dr Miklowitz, University of Colorado at Boulder, Muenzinger Bldg, Boulder, CO 80309-0345 (miklow@psych.colorado.edu).

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1. Birmaher B, Axelson D, Strober M, Gill MK, Valeri S, Chiappetta L, Ryan N, Leonard H, Hunt J, Iyengar S, Keller M. Clinical course of children and adolescents with bipolar spectrum disorders. *Arch Gen Psychiatry*. 2006;63(2):175-183.
2. Keller MB, Lavori PW, Friedman B, Nielsen E, Endicott J, McDonald-Scott P, Andreasen NC. The longitudinal interval follow-up evaluation: a comprehensive method for assessing outcome in prospective longitudinal studies. *Arch Gen Psychiatry*. 1987;44(6):540-548.

Is Elevated Striatal Dopamine Function a Prodromal Sign of Schizophrenia?

It was a pleasure reading the article by Howes et al,[1] who report an increase of striatal dopamine activity in patients fulfilling prodromal criteria for schizophrenia. They demonstrate that striatal dopamine activity was correlated with the severity of prodromal symptoms and with the severity of neuropsychological impairment in subjects with at-risk mental states (ARMS). However, as not all of these subjects go on to develop psychosis, Howes et al propose that elevated dopamine activity may also be a correlate of increased vulnerability to psychosis and conclude that presynaptic striatal function may be a promising target for future drug development in the treatment of psychotic disorders.

Prospective studies of patients meeting ARMS criteria initially reported 1-year rates of transition to psychosis of 40% to 54%, but lately reported rates have dropped to 15%. In our Swiss Bruderholz Study of 196 individuals referred for a suspected ARMS, we have recently shown that patients with ARMS (n=73) score at an intermediate level between a control group and a group of patients with first-episode psychosis on positive symptoms and on a subset of cognitive functions assessed at baseline.[2] At 1-year follow-up, 13.5% of the patients converted to full-blown psychosis, while 60% of the patients fully remitted from initial ARMS (A. E. Simon, MD, and D. Umbricht, MD, unpublished data, December 29, 2008). Neither pharmacotherapy nor psychotherapy received during the 1-year follow-up was associated with recovery from ARMS. Thus, the chance of remission to a nonrisk state was more than 4-fold higher than the chance of conversion to psychosis. Preliminary 2-year follow-up data corroborate high remission rates from an initial ARMS, and very recently, we have demonstrated that in a population of adolescents, hallucinatory phenomena showed high rates of remission at 1-year follow-up.[3] Against this background, the findings of Howes et al[1] suggest that increase of dopaminergic activity may occur as a transitory phenomenon in a substantial number of ARMS.

These findings are noteworthy for at least 2 reasons. First, they support the view that in some individuals with increased vulnerability for transient psychotic symptoms, dopamine activity may increase as a consequence of environmental stressors and cause the positive symp-

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