

It is illegal to post this copyrighted PDF on any website. The Epidemic of Depression With Obesity

Susan L. McElroy, MD

In this month's issue, Olvera and colleagues¹ provide important findings about the increasingly recognized link among depression, obesity, and metabolic syndrome.² Evaluating 1,768 Mexican American adults living on the United States/Mexico border from 2004 to 2010, they found that 30% had current depression, 14% had severe depression, 52% were obese, and 45% had metabolic syndrome. Depression was associated with female gender, low education, low high-density lipoprotein cholesterol, and increased waist circumference, while severe depression was associated with female gender, low education, and extreme obesity. The authors concluded that among Mexican Americans, obesity, female gender, and low education were risk factors for depression.

To provide context, these findings can be compared with data from the National Health and Nutrition Examination Survey (NHANES) obtained during a comparable time period, 2005 to 2010.² As in Olvera and colleagues¹ study, obesity was defined as a body mass index (BMI) ≥ 30 mg/kg², BMI was determined from measured (as opposed to self-report) body weight and height, and depression was defined as exceeding a threshold of depressive symptoms over the past 2 weeks. In that data set, 7.2% had current depression and 34.6% were obese; 43% of adults with depression were obese; adults with depression were more likely to be obese than adults without depression; and the proportion of adults with obesity rose as the severity of depressive symptoms increased. Women with depression were more likely to be obese than women without depression in every age group, while this was true of men only in those ≥ 60 years.

However, among Mexican American women and men, rates of obesity did not differ by depression status in the NHANES data.² The relationship between obesity and depression varied by race and ethnicity only among non-Hispanic white women. Thus, 46.6% of depressed Mexican American women were obese compared with 43.1% of nondepressed Mexican American women, while among non-Hispanic white women, 45% with depression were obese compared with 32% without depression. It is unknown why Olvera and colleagues' findings are inconsistent with NHANES, but they show that the links among depression, obesity, and metabolic derangement are just as relevant to

Mexican American women as they are to other racial/ethnic groups.

What do we know about the depression-obesity relationship? As found by Olvera and colleagues,¹ this relationship appears to be stronger in women than in men and with greater severity of depression.³ Other data show that it is bidirectional⁴ and associated with atypical depressive features.⁵ Thus, obesity increases the risk of onset of depression, and depression predicts development of obesity. A similar bidirectional relationship may exist between depression and metabolic syndrome.⁶

It has been hypothesized that obese individuals may develop depression due to the stigma or medical burdens of obesity, as well as the adverse effects of the proinflammatory state of excess adiposity on the central nervous system. It has been hypothesized that depression causes obesity because of phenomenological similarities, such as overeating, physical inactivity, and disturbed sleep. Indeed, the atypical subtype of major depressive disorder (MDD) is a strong predictor of obesity, including elevated waist circumference, in men and women. In a prospective study of 3,054 randomly selected residents of Lausanne, Switzerland, MDD with atypical features was associated over a 5.5-year period with an increase in adiposity in terms of BMI, incidence of obesity, and waist circumference in both sexes.⁵ This relationship was not explained by sociodemographic and lifestyle characteristics, comorbid mental disorders, use of antidepressant medication, or use of other weight-increasing medications. Moreover, the elevated BMI in individuals with atypical depression persisted after remission of the depressive episode.

Another important contributor to the depression-obesity association may be disordered eating, such as binge eating, night eating, emotional overeating, and grazing. Defined as overeating with a subjective sense of loss of control over eating, binge eating is associated with depression, obesity, and metabolic dysfunction.⁷ Moreover, binge eating among adolescents and loss-of-control eating among children (thought to be a precursor to binge eating) are predictive of overweight/obesity and the onset of depressive symptoms. In a prospective cohort study of 16,882 American adolescents aged 9 to 15 years followed from 1996 to 2005, binge eating (defined as overeating with loss of control), but not overeating without loss of control, was associated with incident overweight/obesity (odds ratio = 1.73; 95% CI, 1.11–2.69) and onset of depressive symptoms (odds ratio = 2.19; 95% CI, 1.40–3.45).⁸

These findings have important public health implications. First and perhaps most important, the medical field needs to firmly accept that obesity is a risk factor for depression

Submitted: December 10, 2014; accepted December 15, 2015.

Corresponding author: Susan L. McElroy, MD, Craig and Frances Lindner Center of HOPE, Research Institute, 4075 Old Western Row Rd, Mason, OH 45040 (susan.mcelroy@lindnercenter.org).

J Clin Psychiatry 2015;76(10):e1340–e1342
dx.doi.org/10.4088/JCP.14com09722

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and, conversely, that depression is a risk factor of obesity. Thus, individuals with obesity, abdominal obesity, or related forms of metabolic dysfunction should be evaluated for depression,⁹ and individuals with depression should have their anthropometric measures and metabolic status determined and monitored. The co-occurrence of obesity and depression, in turn, should trigger an evaluation for atypical depressive symptoms and disordered eating. Second, despite recent findings from NHANES, Hispanic ethnicity should increase focus on evaluating depression and metabolic dysfunction among women with obesity. Third is the issue of screening and prevention. Programs designed to prevent obesity by screening BMI in school children are controversial because of concerns that they might promote reduced self-esteem, distorted body image, and disordered eating behavior.¹⁰ That begs the question, if depression and/or disordered eating were detected and aggressively treated early, could obesity be prevented? In a parallel-group, 12-week randomized trial comparing interpersonal psychotherapy or a weekly health education group in 113 adolescent girls considered at high risk for adult obesity and eating disorders (because of a BMI between the 75th and 97th percentiles and episodes of loss-of-control eating), both groups showed similar improvement in BMI metrics, percent body fat, loss-of-control eating, and symptoms of depression and anxiety over 12 months of follow-up.¹¹ These data suggest that BMI-based obesity prevention programs may need to also address depressive symptoms and disordered eating to be effective and safe.

Yet another important but unresolved issue is whether the management of obesity or MDD differs when the 2 conditions co-occur. Thus, depression with obesity is associated with more severe course of illness and poorer outcome (and possibly even specific neurostructural alterations) compared with depression without obesity, but it is unknown if the 2 clinical situations should be managed differently.¹² For example, obesity treatment guidelines generally recommend that antiobesity medications be discontinued if there has been failure to lose a clinically significant amount of body weight (eg, 3%–5%) within 3 to 6 months. For the obese person with MDD who is actively gaining weight, however, prevention of further weight gain may be an equally important goal.

Unfortunately, there has been scarce research on the treatment of MDD and obesity when both conditions are present. In clinical weight loss trials in obese individuals, behavioral weight loss interventions, including exercise alone, tend to reduce depressive symptoms, but participants' level of depressive symptomatology typically does not rise to a diagnosis of MDD.¹³ Bariatric surgery is considered the most effective treatment for obesity; depressive disorders are common among individuals seeking such surgery; and observational studies indicate that depressive symptoms decrease after surgery. However, improvement in depressive symptoms declines over time, and there is a subset of patients who do not experience improvement.¹⁴ Moreover, depressive symptoms are associated with greater

postoperative complications, less weight loss, and greater weight regain and have been hypothesized to contribute to the elevated risk of suicide observed among bariatric surgery recipients.

Finally, exclusion criteria for rigorously controlled weight loss trials typically include severe mental illness, and it is unknown if their findings can be generalized to the individual who has both MDD and obesity. There are 4 new antiobesity agents that have received approval from the US Food and Drug Administration (FDA) for chronic weight management that may exert their weight loss effects through the central nervous system: the combination of phentermine and topiramate extended release, the serotonin 2C receptor agonist lorcaserin, the combination of naltrexone sustained release (SR) and bupropion SR (NB), and a high dose of the long-acting glucagon-like peptide-1 agonist liraglutide (which is already marketed for the treatment of diabetes at a lower dose).^{15,16} Importantly, none of the treatments appeared to increase psychiatric adverse events to the extent seen with rimonabant, a cannabinoid receptor type 1 antagonist that has been removed from the market because of an increased incidence of anxiety, depression, and suicidal ideation. All 4 agents also reduced waist circumference and improved metabolic factors, such as serum lipids or glycemic profiles.

In the pivotal studies for all 4 compounds, however, people with serious psychiatric illness were explicitly excluded. In the only intervention study of which I am aware that required participants to have both MDD and overweight or obesity, 23 women with MDD and overweight or obesity received open-label treatment with NB for up to 24 weeks.¹⁷ NB reduced both depressive symptoms and body weight at 16 and 24 weeks. Mean \pm SD weight loss was $-4.0\% \pm 4.6\%$ at week 12 and $-5.3\% \pm 6.5\%$ at week 24. NB was also associated with improved self-report ratings of control over eating and binge eating symptomatology. These data are limited by lack of a placebo control but suggest that syndromal depression and obesity may be effectively treated simultaneously.

In short, depression with obesity is an important comorbidity needing vastly more research regarding etiology, prevention, and treatment. Specifically, just as rigorous randomized control trials have been done in obesity with various medical complications (such as diabetes or hypertension), such trials need to be conducted in obese individuals with MDD. Ideally, such trials would also evaluate atypical depressive features and disordered eating, as well as effects on visceral adiposity, cardiovascular parameters, and fasting lipids and glucose.

Author affiliations: Craig and Frances Lindner Center of HOPE, Research Institute, Mason, Ohio, and Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine, Cincinnati, Ohio.

Potential conflicts of interest: Dr McElroy is a consultant for Bracket, F. HoffmanLa Roche Ltd, Shire, and Sunovion; has received grant/research support from Alkermes, Cephalon, Forest, Marriot Foundation, Naurex, Orexigen, Shire, and Takeda; and has been a speaker or on the advisory board for MedAvante, Naurex, Novo Nordisk, Shire, and Sunovion.

Funding/support: None reported.

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