The Co-occurrence of Depression and Obesity:

Implications for Clinical Practice and the Discovery of Targeted and Precise Mechanistically Informed Therapeutics

Roger S. McIntyre, MD, FRCPC

Baek et al in this issue of the *Journal* present results from a longitudinal observational study that aimed to ascertain whether a correlation exists between depressive symptom trajectories and the evolving risk of underweight/obesity.[1] It is a highly replicated finding that a robust, bidirectional, cross-sectional and longitudinal association exists between underweight/obesity and depressive symptoms in both the general and clinical population.[2–7] The Baek et al study extends our understanding of this association by identifying subpopulations of depressed persons, defined on the basis of longitudinal symptom severity, and its relationship with body mass index (BMI; kg/m^2). The impetus provided by the authors to conduct this research was to reconcile apparently conflicting reports in the extant literature wherein both increased and decreased weight in depressed populations have been observed.

The study's data source was the Korean Longitudinal Survey of Women and Families (KLoWF) which originated in 2014 and was completed in 2020. It is notable that South Korea has the highest rate of death by suicide of any member nation within the Organization for Economic Cooperation and Development.[8] The target population of the KLoWF was Korean women aged 19–64 years. A total of 7,691 participants completed the 2014 survey, while 6,196 participants completed the 2020 survey, representing 27,488 observations across a mean 3.45 number of visits per participant. Depressive symptoms were measured with the 10-item Center for Epidemiologic Studies Depression Scale (CESD-10) Korean Version. Obesity and underweight were operationalized as follows: Class I obesity, 25 kg/m^2 ≤ BMI < 30 kg/m^2; Class II obesity, BMI ≥ 30 kg/m^2; and underweight, BMI < 18.5 kg/m^2.

Using growth mixture models, 5 separate depression subgroups (ie, classes) were identified. Of the 5 subgroups identified, persons (N = 279; 3.6%) with persistently high levels of depressive symptoms (CESD-10 score > 10) exhibited an increased adjusted odds ratio (OR) for underweight from 2014 to 2020 from 2.27 (95% CI, 1.32–3.92) to 3.39 (95% CI, 1.91–6.05). In addition, this subgroup was at increased risk for Class II obesity at the 2020 evaluation (OR [95% CI], 3.76 [1.97–7.17]).

This thoughtful analysis by Baek et al has "fit for purpose" implications for clinical practice and raises many interesting questions with respect to mechanistic translational research and treatment discovery. From a clinical perspective, the Baek et al study reminds practitioners that persons living with depressive symptoms are differentially affected by clinically meaningful changes in BMI.[9,10] The novelty of the Baek et al study is the granularity that has been provided insofar as they identified a subgroup of persons with severe persistent depression who were especially susceptible to BMI shifting, warranting a personalized approach with respect to medical risk assessment and care planning.[11]

Their results further augment the evidentiary base that has supported recommendations for the routine assessment of diet, lifestyle, exercise and overall activity, sleep patterns and comorbidity associated with weight change (eg, binge eating disorder, attention-deficit/hyperactivity disorder, and alcohol and/or substance use disorder) as well as BMI and weight-related metabolic comorbidity in all depressed patients.[11,12] Notwithstanding these recommendations, it is disquieting that results from implementation science surveys in psychiatry indicate that most persons with severe persistent illness are not being routinely monitored for metabolic aspects, a modifiable quality of care gap.[13–15] In addition, the greater propensity to clinically meaningful BMI shifting in the severe persistent depression group assigns a higher level of priority to psychotropic

drug selection that is less likely to significantly alter body weight and metabolism.[16]

A separate clinical consideration, which I inferred from the Baek et al study, is that persons with persistently high depressive symptoms and underweight/obesity may be at a higher risk for suicidal ideation and suicide attempts as well as death by suicide. In addition to depression being highly associated with suicidality, replicated and convergent evidence also has documented an association between underweight as well as obesity with suicidality.[17,18] A separate line of research has also reported a further increased risk for suicidality in persons living with mood disorders and comorbid obesity when compared to persons with mood disorders who are not obese.[19]

I have noticed, in accordance with published literature, in my own patients living with depressive or bipolar disorders that general cognitive impairment and aspects of anhedonia are more pronounced when they are either underweight or obese.[20,21] It could be conjectured that the increased risk for suicide in persons with severe persistent depression and comorbid underweight/obesity is partially mediated by cognitive impulsivity and greater impairment in reward function (notably anticipatory anhedonia).[22–27] The link between depressive symptoms, underweight/obesity, general cognitive impairment and anhedonia instantiates the mechanistic "metastasis" of obesity to the brain.[28,29]

From the perspective of mechanistic translational research and treatment discovery, the Baek et al study reminded me of the future research pathway in the development of precise innovative therapeutics in psychiatry. It is a priority research vista in psychiatry to identify mechanistic pathways and hierarchical systems that subserve the surface-based phenomenology encountered clinically. Therapeutic advances in other areas of medicine (eg, cancer) are paradigmatic of the innovation that is possible with therapeutic discovery and development when mechanistically informed approaches are the strategic priority.

The overarching barrier to identifying mechanistically informed and disease-modifying therapies in psychiatry is the incomplete understanding of the causal mechanisms and disease pathogenesis. Depressive disorders are (like all mental disorders) highly heterogeneous with respect to causation, pathoetiology, illness trajectory and response to treatment. Although once considered monocausal, depressive disorders are now conceptualized as multicausal, probabilistic rather than deterministic, and dynamic rather than static phenotypically and biologically throughout the illness trajectory.[30] A single encompassing explanatory mechanistic model of depressive disorders would certainly cater to our appetite for simplicity and brevity but would also strain credulity and validity.

A strategic approach to the aforementioned challenge of heterogeneity is to subphenotype mood disorder populations on the basis of observable characteristics and biomarkers/biosignature (ie, phenobiotype).[11,31] For example, persons with depressive disorders may be subtyped on the basis of phenotypic (eg, anhedonia, general cognitive impairment, and underweight/obesity) and/or illness course characteristics (eg, longitudinal symptom severity). A subphenotyping approach identifies "latent" subpopulations with less neurobiological heterogeneity, which is sine qua non for parsing underlying neurobiological mechanisms relevant to the disease process.

For example, one could conjecture that the subpopulations in the Baek et al study with severe persistent depression were more likely to evince alterations in sympathetic and hypothalamic-pituitary-adrenal activity, proinflammatory imbalance and/or insulin-glucose dysregulation.[32–46] If so, this might implicate a subpopulation of adults with depression as having a phenotype that is best conceptualized as a "metabolic-inflammatory" depression.[39] A derivative of these observations and assumptions is that treatment discovery and development for depressive disorders could involve de novo or repurposed drugs that heretofore have been implemented in persons with metabolic and/or inflammatory disorders.

For example, glucagon-like peptide-1 (GLP-1) is a protein produced by L-cells of the intestine, as well as in neurons located in the nucleus tractus solitarius. In addition to increasing insulin biosynthesis and release in response to an oral glucose load, GLP-1 decreases glucagon, gastric motility and appetitive drive.[47] GLP-1 receptor agonists (GLP-1 RAs) are approved as glucose-lowering agents and for weight management in persons who are overweight with associated metabolic morbidity, or obese. In addition to their effects on metabolics and weight, GLP-1 and GLP-1 RAs are nerve growth factors that have been shown to increase dendritic length, branching, and complexity as well as augment neuroplasticity via glutamatergic, monoaminergic, anti-inflammatory, and antioxidative pathways.[48–51]

Available evidence also indicates that GLP-1 RAs may also selectively target brain regions implicated in both obesity and depression. For example, the habenula, also known as the "antireward" center, is implicated in the pathogenesis of depressive disorders and obesity and is also a region targeted by GLP-1 RAs.[52,53] A separate observation is that GLP-1 RAs exert effects on brain connectome relevant to both

depressive disorders and obesity.[54] The combined GLP-1/glucose insulinotropic polypeptide (GIP) receptor agonist (ie, tirzepatide) may result in more pronounced weight loss relative to GLP-1 RAs, and separately, it has been shown that GIP has direct neurotrophic effects in the brain.[55]

The foregoing concatenation of study findings with GLP-1 RAs may provide some understanding of the mechanisms mediating the reduction of depressive symptoms and cognitive dysfunction reported in persons prescribed these agents principally for a metabolic disorder or obesity.[56,57] The separate observation that GLP-1 RAs are brain-penetrant provides the basis for repurposing these agents in the prevention and/or treatment of psychiatric disorders, including depressive disorders, major neurocognitive disorders (eg, Alzheimer disease), Parkinson disease, traumatic brain injury and alcohol use disorders.[56,58]

As with all studies, there are methodologic aspects to the Baek et al study that affect inferences and interpretations of their findings. I did wonder whether potential anamnestic factors, notably childhood adversity and trauma, may have been an antecedent cascade event igniting biological processes that predispose and portend the symptom trajectories that were observed (ie, severe persistent depression) as well as underweight/obesity.[59] In addition, data were not available with respect to symptom profiles of the participants and its potential association with change in BMI. Replicated evidence indicates that atypical depressive symptoms, notably increased appetite, and food consumption in persons with depression have a greater association with anthropometric change and may have a distinct neurobiological mechanism.[35,36,60]

A further consideration is whether the change in BMI observed by Baek et al may have been in part a consequence of psychotropic drug exposure. My own observation clinically, and shared by many others, is that persons with more severe persistent depression are much more likely to find themselves in a futile therapeutic odyssey of exposure to often inadequate, weight gain–promoting psychotropic drugs, especially when their illness is much more resistant to monoaminergic agents.[16]

A separate but related consideration is that persons who are underweight/obese are more likely to evince lower remission rates when prescribed selective serotonin reuptake inhibitors when compared to persons who are normal weight. With this in mind, I wondered whether some of the persons in the Baek et al study in the severe persistent depression group were treatment-resistant to monoaminergic drugs which predisposed polypharmacy. Indeed, treatment-resistant depression (TRD) is much more likely to be observed in persons with obesity, and conversely, the risk for obesity and associated morbidity is significantly more likely to manifest after the diagnosis of TRD.[12,61]

Psychiatry has entered a very exciting and hopeful time. Rather than depending on serendipitous observations as our strategy for therapeutic discovery and development, the field is identifying therapeutics on the basis of phenobiotypes and postulated mechanisms of disease. For example, the *N*-methyl-D-aspartate receptor antagonist esketamine for TRD and depression at imminent risk for suicide, the γ-aminobutyric acid positive allosteric modulators brexanolone and zuranolone for postpartum depression, and dual orexin receptor antagonists suvorexant, lemborexant, and daridorexant as well as the anti-amyloid-β lecanemab for the treatment of cognitive impairment in Alzheimer disease represent examples of clinically available mechanistically informed therapeutics in psychiatry.[62–66]

In addition to these examples, there are many other innovative therapeutic strategies for psychiatric disorders that are in early-late-stage development that are targeting systems known to be mechanistically mediating psychopathology [eg, κ-opioid receptor antagonists, potassium voltage-gated channel subfamily Q (KCNQ) openers, and selective orexin-1 receptor antagonists].[67] It is my hope that this innovative approach, which begins with careful phenobiotyping, will end the waiting for so many persons living with depressive disorders looking to have their life back.

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Author Affiliations: Department of Psychiatry, University of Toronto, Toronto, Canada; Department of Pharmacology, University of Toronto, Toronto, Canada; Brain and Cognition Discovery Foundation, Toronto, Canada.

Corresponding Author: Roger S. McIntyre, MD, FRCPC, Brain and Cognition Discovery Foundation, 77 Bloor St W, Ste 617, Toronto, ON M5S 1M2, Canada (roger.mcintyre@bcdf.org).

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