The following is the highest rated article in our 2019 submission category *Future Medicine & Treatment*. All articles were ranked by HSI's independent professor judging panel. For this, the author was awarded one of three of HSI's annual "scholarship" awards.

Health Science Inquiry

Precision Medicine Targeting the Gut-Brain Axis in Depression: The Future of Psychiatric Treatment

Caroline Wallace[1]

[1]Centre for Neuroscience Studies, Faculty of Health Sciences, Queen's University

Precision medicine is becoming increasingly popular in the healthcare setting in an attempt to treat illness more effectively. The term precision medicine refers to prevention and treatment strategies that are based on individual variability and targeted toward precise molecular underpinnings of disease [1], as opposed to using a standardized or 'one size fits all' model. Precision medicine aims to treat individual patients using approaches that have been identified as being effective based on specific characteristics, including biological and psychosocial markers. It is a model that makes use of data, analytics, and information, and pays significant attention to patient engagement, digital health, genomics, and data science [2]. Precision medicine is already in practice for some illnesses such as breast, lung, and colorectal cancers, and now neuroscientists are exploring precision medicine in neurological diseases, including Parkinson's Disease and Alzheimer's Disease. These diseases have been proposed as ideal for realizing precision medicine due to their strong genetic component [1], and this research is beginning to be extended into psychiatric diseases as well, including Major Depressive Disorder (MDD).

MDD is a psychiatric disease characterized by a persistent feeling of sadness or lack of interest accompanied by other psychological and physiological symptoms that impair daily functioning. MDD is an ideal candidate for precision medicine due to the heterogeneity in clinical presentation and pathophysiology of the disorder. For example, consider two fictional patients, Patient A and Patient B. Patient A presents with low mood, lack of energy, sleeping 12-16 hours a day, increased appetite and weight gain, and suicidal ideation. Patient B presents with loss of pleasure or enjoyment, feelings of extreme guilt, loss of appetite and weight loss, agitation and severe insomnia. Both patients are diagnosed with MDD yet have no overlapping symptoms. This heterogeneity of symptomatology may translate to a heterogeneity in pathophysiology. Research has identified common neurophysiological changes associated with the disorder, including alterations in neurotransmitter functioning and neuroinflammation [3], but the degree of these changes varies widely across patients, as does the etiology of the disorder. While patterns exist, explicit causes of MDD remain unclear and questions regarding etiology persist: Why do some individuals who have experienced adverse childhood experiences become depressed, while others do not? Why do some individuals who objectively lead stable and comfortable lives become depressed, while others do not? Ongoing research into symptomatology, pathophysiology, and etiology have aided in the development of antidepressant medication. However, the response to treatment in MDD varies widely; Many patients try two to three different medications before finding one that works, and even then, up to 60% of patients discontinue their antidepressant use within the first three months due to issues such as side effects [4]. It is impractical to attempt to treat individuals universally, and thus more precise treatment strategies are warranted.

The Canadian Biomarker Integration Network in Depression (CAN-BIND) program is a leader in the initiative to identify biomarkers that will help predict who and how individuals will respond to various available treatments. CAN-BIND studies examine different treatment strategies and collect data based on several platforms, including clinical, molecular, neuroimaging, mobile-health technology, and use an informatics-based approach to integrate this data to stratify depressed patients into subgroups based on specific characteristics. This information can then be used to optimize treatment using precision medicine by identifying to which subgroup a patient belongs and using the corresponding treatment shown to be efficacious for that subgroup. One treatment strategy being explored within the CAN-BIND network is targeting the gut-brain axis using probiotic intervention. The gut-brain axis is a bidirectional communication network between the brain and the gastrointestinal (GI) tract that communicates via the autonomic nervous system, the enteric nervous system, the neuroendocrine system, and the immune system [5]. The gut-brain axis has been implicated in the pathophysiology of MDD as a potential molecular underpinning to the disease [6]. This has led to the investigation of probiotics, bacteria in the GI tract that confer a health benefit to the host, as a potential treatment for MDD [7]. While research to date on probiotics improving symptoms of depression

in MDD patients is scant and inconclusive, research on healthy humans has shown improvements in mood and affective symptoms following probiotic supplementation [7]. The composition of the microbiome that colonizes the GI tract is unique to each individual, and it has been shown that depression is associated with reduced diversity in the microbiome of the GI tract [8]. Thus exploring how depressed individuals respond to probiotic supplementation may provide crucial insight into those important questions on the etiology, pathophysiology, and symptomatology of MDD.

The collection of biospecimen samples such as blood, stool, and urine as part of the molecular platform will allow us to obtain biological information that may reveal certain genes, proteins, inflammatory markers, or bacterial products that may correlate to treatment response. For example, if probiotic supplementation does indeed alleviate symptoms of depression, but only in patients who present with high plasma levels of lipopolysaccharide (LPS; an innate immune-activating endotoxin that may have a role in gut-brain signaling), this would present a valuable opportunity for applying precision medicine: a blood test screening for LPS levels could determine whether a patient will respond. It is also important to note that biomarkers do not necessarily have to be biological, they can be psychosocial or behavioural, collected as part of the clinical and m-health platforms: if it is determined probiotic supplementation alleviates symptoms of depression but only in people who engage in a certain level of physical activity weekly, patients could be screened for physical activity to determine if the treatment will work for them.

The medical model of precision medicine allows physicians to customize healthcare by selecting treatments that are the most likely to benefit the patient. However, it does not come without its drawbacks. Precision medicine strategies may be costlier and more time consuming. It has been argued that precision medicine is not ideal for high-prevalence diseases and disorders; more rapid and low-cost standardized treatments that cover more bases should be pursued first. However, in psychiatric disease where the precursors and outcomes can be so variable, it may be more effective in reducing the time between diagnosis and relief of symptoms. With this as the main goal in mind, the future of psychiatric treatment could very well be clinicians and neuroscientists working collectively to apply precision medicine techniques to MDD to improve prognosis by identifying individual patterns of risk factors, symptoms and pathophysiology.

References

[1] Tan L, Jiang T, Tan L, Yu JT. Toward precision medicine in neurological diseases. Annals of translational medicine. 2016;4(6).

[2] Ginsburg GS, Phillips KA. Precision medicine: From science to value. Health Affairs. 2018;37(5):694–701.

[3] Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nature reviews immunology. 2016;16(1):22.

[4] Lingam R, Scott J. Treatment non-adherence in affective disorders. Acta Psychiatrica Scandinavica. 2002;105(3):164–172.

[5] Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nature reviews neuroscience. 2012;13(10):701.

[6] Foster JA, Rinaman L, Cryan JF. Stress & the gut-brain axis: regulation by the microbiome. Neurobiology of stress. 2017;7:124–136.

[7] Wallace CJ, Milev R. The effects of probiotics on depressive symptoms in humans: a systematic review. Annals of general psychiatry. 2017;16(1):14.

[8] Kelly JR, Borre Y, O'Brien C, Patterson E, El Aidy S, Deane J, et al. Transferring the blues: depression-associated gut microbiota induces neurobehavioural changes in the rat. Journal of psychiatric research. 2016;82:109–118.

Caroline is a PhD Candidate in Clinical Neuroscience at Queen's University. Her research interests currently lie in examining the neurobiological relationship between nutrition and mental health to develop novel treatments for depression, as well as searching for biomarkers that will help predict who will respond to these treatments. Her doctoral research involves running a clinical trial examining the effects of a probiotic supplement on symptoms of depression, and how inflammation may be mediating this relationship.