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Practice

The Gut Microbiome and Mental Health

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Abstract

The gut microbiome has been well researched in the past few years and may be a target for treating mental illness. Trillions of bacteria in the digestive system work with the brain, immune function, and endocrine pathways. This gut microbiome ecosystem mediates the interaction between the human being and the environment making its inclusion in holistic nursing essential. Changes in normal balance of the gut microbiome occur with diet, antibiotics and other medications, stress, cancer treatment, geography and environment, and current illnesses. When the microbiome is challenged a "dysbiotic" state leads to inadequate production of needed neurotransmitters such as serotonin and dopamine. Research has shown links between the dysbiosis, and the inflammatory response system that are known to contribute to depression, anxiety, and schizophrenia. Understanding the role of the gut microbiome can be beneficial to holistic nurses, providing a new tool to prevent, treat, or reduce symptoms of mental illness and improve general immune function. This innocuous holistic approach to mental wellness is becoming an important evidenced-based approach.

Keywords

gut microbiome, schizophrenia, depression, anxiety, inflammation, dysbiosis

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Biomedical/western medicine is only about 300 years old and was founded on the beliefs of René Descartes: the mind and body are completely separate entities. And to further complicate application of holistic care, it was believed that to understand a phenomenon, only objective, quantitative data was relevant. Since much of human experience is subjective and not measurable, phenomena such as emotions, stress, social support, or beliefs became irrelevant to physical health. Descartes and later Sir Isaac Newton (1642–1727) believed that the universe is like a large mechanical clock, where everything happens in a linear sequential form. This mechanistic approach objectively views and measures the human body parts. It was believed that if you could look at the parts, you would understand the human body. This reductionism is still the approach used to diagnose and treat in Western medicine. The person is converted into increasingly smaller components, systems,

organs, cells, and bio-chemicals, any level of which might break down. This Cartesian duality got us to a place in history where we are still trying to reconnect the mind and body in concept, diagnosis, and treatment.

Nursing theory gives inspiration to think creatively, outside the box. Since Nightingale (1860) we have understood that holistic nursing care is more than treating a condition. The whole person's healing is influenced by everything around them, including light, cleanliness, and fresh air (Nightingale, 1860). Over time holistic nursing has evolved its definition (Gullett et al., 2022). The term *bio-psycho-social* was found to be wanting because this way of thinking was still reductionist and does not consider the environment, spiritual experience, or the connections between experience and biology, such as long-term health consequences of trauma. The boundaries of health and disease fall outside the biopsychosocial model. For a few years, the term was changed to bio-psycho-social-spiritual but was still criticized for being reductionist and missing other relevant interactions (education, work, cultural meaning, the environment, health policy). Psychoneuroimmunology, the science behind holistic health approaches has also struggled with its identity with some suggestion to changing the field to psycho-neuro-endocrine-immunology. This was still criticized as a reductionist approach that was missing not only many other parts, but the whole (Wilson, 2022).

The term *holistic* makes the most sense, where the nurse is keeping the patient at the center of care and considering everything that influences this patient on any level. A core value of the American Holistic Nurses Association standards of practice is to incorporate an understanding of the environment (Mariano, 2022). This environment, including the gut microbiome, encompasses everything around the patient that may influence health and examining these interactions helps illuminate patterns around illness (Mariano, 2022). Looking at the microbiome as a separate part, *other* than self, makes sense at first thought, but this doesn’t fit. This complex living symbiotic group of microorganisms in the digestive system is part of human behavior, feelings, and health (and more) and in turn is influenced by a person's choices in diet, medication, lifestyle, and stress (and more).

Mental Illness and the Gut Microbiome

One in every eight people in the world lives with a mental disorder (WHO, 2022). The 2019 Global Burden of Disease report found that mental disorders remained among the top ten leading causes of disease burden worldwide. There was a 48.1% increase in mental health disorders between 1990 and 2021 (GBD 2019 Mental Disorders Collaborators, 2022). Prevalence of schizophrenia, bipolar, and severe mental illness remained stable, but the burden score of these diseases is among the highest awarded because of the associated profound life quality issues. Depression, anxiety, schizophrenia, and other conditions are targeted with potent drugs that *may* alter neurotransmitter action or levels but leave behind significant and sometimes debilitating side effects. Drugs and therapy are the most common treatment approaches. Holistic nurses recognize that this approach is reductionist, and we are missing essential elements that interact between the mind and body and environment. Teaching the patient about changing lifestyle factors such as stress management, diet, exercise, and improving social support are still essential to holistic care. Targeting the symbiotic microbiome system as a new treatment approach is becoming better understood as more research is published. Caring for the whole patient, including the organisms living within and on the body, just took on new meaning for holistic nurses. The purpose of this practice article is to share current understanding of the gut microbiome and its applications to holistic mental health nursing practice.

The human digestive system contains trillions of bacteria, fungi, and other microbes that are essential to and symbiotic with human function. There are more bacteria than human cells in the body, and we are more

bacterial than human (Sender et al., 2016). Microbes are found on external and internal surfaces including the conjunctiva, skin, scalp, dental plaque, saliva, and oral mucosa. The majority of microbes and the ones most commonly studied, can be found in the colon (Sender et al., 2016). These complex interactive microbes help digest food, release biochemical byproducts such as neurotransmitters and interact with immune function. When this symbiotic system is out of balance, *dysbiosis* occurs (Figure 1).

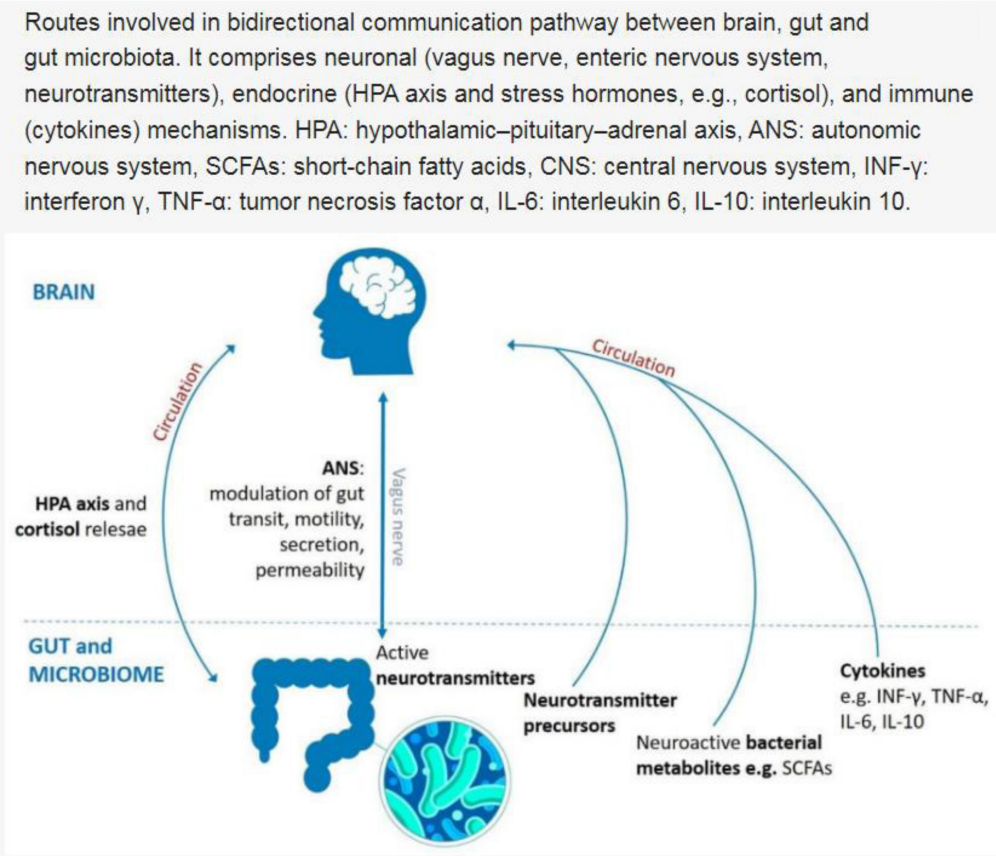

Figure 1. Https://www.mdpi.com/2218-273X/11/7/1000/htm

There is growing evidence that an unbalanced gut microbiome has an influence on behavior through the brain-gut-microbiome axis and this research reinforces the importance of a holistic view of mental illness. This axis is where the microbial flora, endocrine system, immune system, sympathetic and parasympathetic systems, and the rest of the central nervous systems interact. Understanding the role of the gut microbiome will help illuminate ways to prevent, treat, or reduce symptoms of mental illness. Armed with a better understanding of how the molecules produced by the gut microbiome can be tailored to improve immune system signaling, inflammation, neurotransmitter levels, behavior, and mental health, a holistic nurse can add another topic of patient teaching to the toolbox. Literature/research published since 2018 in nursing, biology, and psychology journals provided over 90,000 results, showing the plethora of current studies and importance of the topic.

Searches for this paper included the key words “gut microbiome, microbiota, depression, schizophrenia, anxiety, and mental health”.

The Gut Microbiome

Probiotics are the active bacteria and other microbiome that are added to the diet, yogurt, or supplements, for example. Prebiotics are non-digestible compounds that are degraded by these bacteria in the GI tract. Prebiotics are known to enhance the growth of endogenous beneficial bacteria, *lactobacilli* and *bifidobacterial* for example. Bacterial fermentation and breakdown of prebiotics results in the production of short-chain fatty acids (SCFA) that can be linked to their beneficial effects (Davani-Davari et al., 2019). See Table 1 for examples.

Table 1. Partial List of Probiotics (Foods That Contain Healthy microbiota) and Prebiotics (Foods That are Needed for microbiota to Survive)

Probiotics Examples List
yogurt, pickles, miso, kimchi, sauerkraut, kefir, certain cheese, supplements
Prebiotics Examples List
bananas, fiber, whole grains like barley, wheat, and oats, flax seeds, garlic, chicory root
for more information on the use of pro- and prebiotics (NIH, 2019).

The gut microbiome includes various yeasts, protozoa, viruses, parasites, and other micro-organisms, but studies have mostly focused on the bacterial population. Current research is illustrating the connections between the gut microbiome and numerous specific illnesses. Treatment approaches are changing. It may not be surprising that an unbalanced gut microbiome is associated with irritable bowel syndrome, or that dysbiosis influences numerous other aspects of health. Because of the brain and gut connections, dysbiosis is also clearly associated with mental illnesses. As background to understanding, an examination of the development of a gut microbiome follows.

The Development of the Gut Microbiome

After the amniotic membranes rupture, an infant is exposed (usually for the first time) to uterine, vaginal, and skin microbes (Zheng et al., 2020). The development of the gut microbiome in an infant is influenced by numerous factors. These may include whether or not the baby was born by caesarian section, breastfed, on medications such as antibiotics, or has inadequate fiber in the diet (Zheng et al., 2020). Fiber is fermented by

bacteria, and the end result is short-chain fatty acids. These molecules are essential to health and play a role in communication with the nervous and immune systems. Fiber is an example of a prebiotic.

Babies born vaginally are exposed to skin microbes that get into the mucous membranes of infant's mouth, anus, vagina, and become part of their own gut microbiome. Babies born by caesarian section (C/S) are at a disadvantage without this exposure, and to compound this, they are more often exposed to antibiotics (Song et al., 2021). Those C/S babies show an imbalance in their microbiome (Hoang et al., 2020). Research is being done on deliberate “seeding” of the baby's mucous membranes with vaginal swabs from the mother but there is not yet enough evidence to recommend this practice (Hoang et al., 2020; Song et al., 2021).

The gut microbiome has already influenced practice for years. For example, Vitamin K is needed for the body to make the proteins needed for blood clotting. Vitamin K is obtained from the excretion of microbiota after digesting meats, fiber, or fermented foods. Because infants are born from a (relatively) sterile environment, they do not have the needed bacteria and other microbes in their gut. Infants are given a boost of Vitamin K at birth until they can get their own gut microbiome primed and begin producing their own. Pro- and prebiotic therapies for the infant have also been considered, but once again, there is not enough research yet to change practice guidelines (Hoang et al., 2020; Song et al., 2021).

The gut microbiota plays a role in many disorders because it is one of the body's most extensive interfaces (are estimated at 250–400 m^2) between the host, environmental factors, and antigens (Buffington et al., 2016). The human gut intestinal microflora is a complex ecosystem containing over 400 bacterial species. The gut microbiome's role in health and disease has been the subject of extensive research, establishing its involvement in human metabolism, nutrition, physiology, and immune function (Buffington et al., 2016).

Call out:

Numerous gut bacteria have been identified, but common players are *Bifidobacterium, bacteroides, f. prausnitzii, firmicutes, and roseburia hominis*

Some of the first microbiomes are *bifidobacterium* that aid in digesting breastmilk. As children grow, the gut microbiome diversifies. Some of these healthy bacteria digest fibers and produce essential fatty acids that are absorbed and contribute to brain and cell growth (Zheng et al., 2020). Diet is fundamental to exposure to and interaction with the environment. Many essential nutrients cannot be synthesized or absorbed without the assistance of bacteria in the gut. The body responds to the environmental microbes, develops a healthy gut microbiome, and thus, a healthier immune system. Currently we understand that the gut microbiome is a key factor in inflammatory bowel disease, cancer, diabetes, dementia, allergy, and rheumatoid arthritis influencing both the start of the disease and intensity of symptoms (Wiertsema et al., 2021; Zheng et al., 2020). These are all examples of autoimmune diseases associated with inflammation (Wilson, 2022). Improving the gut microbiome has been shown to improve symptoms of these diseases, reduce allergic response, and reduce inflammation.

Immunity, Inflammation, and the Microbiome

From birth, the developing immune system has involved the gut microbiome. It is estimated that 70% to 80% of immune cells are in the gut and the interactions between the gut and systemic immune function significant (Wiertsema et al., 2021). These healthy microbes teach the immune response to distinguish between dangerous pathogens and microbes that benefit health. The gut microbiome is intricately involved in the development of both innate and adaptive immunity.

When *good* bacteria are scarce, *bad* bacteria can flourish. For example, *Fusobacterium nucleatum* is strongly associated with colorectal cancer (Cancer.gov, 2022). NCI-funded research indicates that this bacterial

species affects the activity of both innate and adaptive immune cells, leading to the development of an immunosuppressive tumor microenvironment and promoting colorectal cancer progression. Scientists are using this knowledge to develop cancer prevention and treatment strategies aimed at disrupting the effects of this bacterium (Cancer.gov, 2022).

Inflammation, when it is an abnormal, lingering immune response, is influenced by the gut microbiome. Dysbiosis triggers cytokine release and these messenger proteins tell the immune system to generate inflammatory factors, as if there was an injury (Allaband et al., 2018). Gut microbiota imbalance also contributes to intestinal permeability, which in turn leads to numerous health issues. For example, being obese is associated with low grade inflammation, increased permeability, and impaired immune function (Allaband et al., 2018). Certain bacteria are known to trigger inflammatory molecules (like cytokines) that may bring about inflammation in various body tissues. This inflammatory process is triggered by structural components of the bacteria that results in a cascade of inflammatory pathways involving interleukins and other cytokines (Allaband et al., 2018; Wilson, 2022)

Most chronic and autoimmune diseases are a result of low-level systematic inflammation that trigger the disease or its symptoms (Wilson, 2022; Zheng et al., 2020). There is an essential balance of the microbiome that either keeps the immune system in balance, or impairs immune function, triggers inflammation, and leads to autoimmune disorders (Zheng et al., 2020).

Brain-Gut-Microbiome Axis

Complex communication occurs between the gut microbiome and the brain and its role is to integrate gut function, motivation, affect, and cognition. It does this through many bi-directional routes including the vagus nerve, inflammatory triggers such as cytokines, the central nervous system, and the stress responses like cortisol. Other interactions include responses of the sympathetic nervous system, intestinal permeability, intestinal motility, secretion, and the variety and number of microbes (Wiertsema et al., 2021). Numerous studies in “germ free” mice have found that lack of microbes leads to changes in neurotransmitter levels, delayed gastric emptying, behavioral and sleep changes, and inadequate enzymes needed for digestion. These anomalies are reversed after the mice are exposed to microbes to improve their gut health (Wiertsema et al., 2021; Zheng et al., 2020).

The Gut Microbiome and Mental Health

Gut microbiota has been considered not only as a treatment approach but have been implicated in triggering the development of mental health issues. Thinking about mental health through only a non-holistic psychological/cognitive lens would miss this important element. Gut microbes are needed to produce neurotransmitters. As in the example of Vitamin K above, the gut microbiome produces many essential molecules and enzymes needed by the body. Neurotransmitters are produced through or with microbes. Ninety percent of the body's serotonin is synthesized through microbes in the digestive system and serotonin levels are the target of most anti-depressive drugs (Liu et al., 2020). Serotonin has a well confirmed role in sleep and in depression, eating disorders, bipolar disorders, and other mental health disorders. Other neurotransmitters are known to have a role in other mental health disorders such as dopamine in schizophrenia. Specific gut microbiota generate and regulate serotonin, dopamine, norepinephrine, histamine, GABA, and more than 60 other neurotransmitters known, so far (Liu et al., 2020). These symbiotic microscopic symbiotic partners take in fiber and other dietary elements and give out required neurotransmitters and enzymes. For example, humans

could not break down the tryptophan from turkey to build serotonin without their action. There are beneficial and non-beneficial microbes.

Depression

Depression is a leading cause of global disability (GBD 2019 Mental Disorders Collaborators, 2022). Psychotherapy and anti-depressants that seem to target neurotransmitter levels and function have been found to be the most effective treatment. However, medications do not always work, have side effects, and need careful, slow changes to find the right medication and dosage. It is also known that depression is associated with higher levels of inflammatory blood markers (such as cytokines). Thinking about depression as an inflammatory disease changes the old paradigm that it is a psychological sadness and fatigue illness. Neurotransmitters levels associated with depression that are significantly influenced by the gut microbiome are dopamine, norepinephrine, and serotonin (Chudzik et al., 2021; Doll et al., 2022).

Probiotic use in human and animal studies shows reductions in depression and anxiety, similar to levels of antidepressants and other traditional approaches (Davani-Davari et al., 2019). Clinical and experimental studies have demonstrated that gut microbiota play a crucial role in brain function and behavior beyond the development of neurotransmitters. It is known that specific gut microbiota are associated with the pathogenesis of several neurodegenerative and neuropsychiatric disorders such as Alzheimer's disease (AD), anxiety, autism, and major depression (Davani-Davari et al., 2019; Muhle et al., 2018). These studies suggest a strong connection between the gut microbiome and behavioral disorders in mice.

Also relevant for holistic nurses in practice to know is that long-term use of most antidepressants is associated with alterations of the gut microbiome that dampen the benefits of the medication and reduce resistance to bad bacteria such a *C. diff* (*Clostridioides difficile)* that causes diarrhea (Chudzik et al., 2021). The addition of *Lactobacillus rhamnosus* was shown to reduce stress related cortisol (stress) levels and depressive behaviors (Lee & Kim, 2021). There have been numerous other studies examining probiotics, inflammation, and other biomarkers of depression and the role of dysbiosis in triggering depression (Doll et al., 2022). Current research supports the addition of probiotics for a patient being treated with antidepressants (Chudzik et al., 2021).

Anxiety and the Gut Microbiome

Generalized anxiety disorder is characterized by excessive worry, intrusive thoughts, and can be accompanied by physical symptoms (sweating, shaking, increased heart rate) (GBD, 2022). Alterations in the composition of the gut microbiome contribute to psychological changes and symptoms of anxiety. In individuals with generalized anxiety disorders, stool samples revealed reduced bacterial diversity (Chen et al., 2019). Similar findings were noted in those with obsessive compulsive disorders (Chen et al., 2019). The gut microbiome contributes to the construction and regulation of neurotransmitters (for example, GABA, dopamine, and norepinephrine) that are altered in anxiety.

Treatments targeted at correcting the composition of the gut microbiome may prove effective in the treatment and management of anxiety disorders and recommendations for diet and probiotics are within the practice of holistic nurses. Healing the gut microbiome through probiotic and nutritional interventions results in improvement in anxiety symptoms (Yang et al., 2019). The addition of *Lactobacillus* and *Bifidobacterium* was found to provide an anti-anxiety benefit through production of GABA, Serotonin, and by dampening the HPA axis /stress response (Akkasheh et al., 2016). The same studies noted that after treatment with a probiotic, individuals experienced positive neurological changes that included increased BDNF proteins, increased

circulating glutathione, and reduced inflammatory markers (Akkasheh et al., 2016). Further research demonstrates that probiotic therapy over 28 days improved symptoms of anxiety and overall mood (Lee & Kim, 2021). The addition of *Lactobacillus rhamnosus* was also shown to decrease stress-induced corticosterone and reduce anxiety and depressive behaviors (Lee & Kim, 2021).

There is a growing body of evidence that supports probiotic supplementation with specific bacterial strains in the standard treatment of anxiety disorders. Altering the gut microbiome can help to alleviate gastrointestinal symptoms associated with anxiety disorders along with intrusive worry and fear. More research is needed to further identify appropriate strains and dosages to guide holistic nurses in their practice, but treatment incorporating regulation of intestinal flora may prove to be an essential piece in the treatment of anxiety.

Schizophrenia and the Gut Biome

Schizophrenia is a chronic, severe, mental health disorder characterized by alterations in mood, thought, and behavior. Individuals diagnosed with schizophrenia are faced with challenges in managing symptoms of psychosis along with depression and anxiety. Despite available treatment with antipsychotics, residual symptoms remain and can prove difficult to manage. Medications are difficult to tolerate. Due to the need for further treatment options, research is currently being directed in gaining a greater understanding of the role of the brain-gut-microbiome axis in the pathogenesis and progression of schizophrenia (Dinan & Cryan, 2018).

There are significant alterations in the gut microbiome in individuals with schizophrenia, such as decreased gut microbiota richness, elevated gut IgA levels leading to altered glutamate metabolism, and an abundance of *Megasshaera* and *Clostridium perfringens* (Shen et al., 2018; Xu et al., 2020). These alterations lead to stress-induced inflammation, changes in cognition, and noted behavioral changes (Xu et al., 2020). Gut microbial diversity can be interrupted when exposed to infections, maternal stress, dietary changes, antibiotic use, trauma, and individual stress, all of which have previously been noted as risk factors in the development of schizophrenia (Shen et al., 2018; Xu et al., 2020).

The knowledge that gut dysbiosis contributes to altered immunity and inflammation as well as behavioral changes reminds practitioners of the importance of a holistic approach. Restoring the gut microbiome may prove beneficial in treating schizophrenia. Several research studies have looked at the addition of prebiotics, probiotics, and nutrition interventions (Dickerson et al., 2017; Kao et al., 2019). The addition of specific strains of probiotics (eg. *L. Rhamnosus strain GG and B. animalis subsp. Lactis strain Bb12*) to an antipsychotic regimen resulted in improved gastrointestinal symptoms and increased levels of BDNF (Dickerson et al., 2017). These probiotics also lowered *C. albicans* antibodies and led towards improvement in Positive and Negative Syndrome Scale for schizophrenia (Dickerson et al., 2017). Utilizing probiotics in conjunction with antipsychotics (traditional treatment) can help to mediate the effects on the gut microbiome because of antipsychotic therapy and aid in symptom reduction. The addition of probiotic regimen with olanzapine decreased weight gain and the induction of beneficial bacteria improved symptoms (Kao et al., 2019). Elevated levels of *Candida Albicans* in patients with schizophrenia and the addition of probiotic treatment significantly reduced antibody levels and provided some relief of psychiatric symptoms (Dickerson et al., 2017). These facts are essential to patient teaching to help motivate and maintain changes.

Although research is limited it is growing quickly. Preliminary data suggests that alteration in the gut microbiome may be a contributing factor to the pathogenesis of schizophrenia. Addressing the gut microbiome is likely to be a treatment addition for individuals with schizophrenia. Probiotic or prebiotic supplementation may reduce symptoms of psychosis and help to mediate the effects of antipsychotics on the gut microbiome. Further research is needed, as it is not known which specific probiotics or dosages are needed to give specifics

to holistic nurses in practice. Recommending foods high in pro- and pre-biotics are appropriate. Long-term studies are needed to further examine the relationship between schizophrenia and the gut microbiome and to better guide holistic nursing practice.

Nursing Implications

Diet is one of the most effective regulators of gut microbiota. Patient teaching should begin but recommendations on type, source, and amount of pro- or prebiotics need to be better defined for practising holistic nurses. The consumption of pre- and probiotics can have a beneficial effect on the health of the host when administered in adequate amounts. The possibility of modifying the gut microbiota to replace harmful bacteria with more favorable microbiota has been researched since 1907 where we learned that consumption of fermented products containing *Lactobacillus bulgaricus* was associated with longevity and good health (Buffington et al., 2016). Holistic nurses are in a position to provide education on eating foods that promote a healthy gut microbiome to all patients and their families throughout their lifespan.

Nurses may not be aware that fecal transplants are evidenced-based practice, used to treat reoccurring infections with *C. Diff.,* for example (Johns Hopkins, 2022). Feces microbiota from healthy subjects are inserted into the colon of the patient. Fecal transplants are becoming more common for cancer, autism, depression, and a score of autoimmune diseases (Doll et al., 2022; Meyyappan et al., 2020; National Cancer Institute, 2021). There are other methods of transferring healthy bacteria including orally, but more research is needed.

Conclusion

Research presented in this paper connected the dysbiotic state to immune imbalance, inflammation, depression, anxiety, and schizophrenia. Separating mental illness from physical illness limits the holistic approach. This paper only touches on some of the mental health issues being discussed in relation to the gut microbiome. The gut microbiome is complex and has an established role in the development of Alzheimer's disease, cancer, diabetes, vascular dementia, irritable bowel disease, and other autoimmune diseases. It is still unknown which pre- and probiotics are helpful and which are not for specific conditions. Dosage is not tested or regulated, and more research is needed. We need to better understand which microbiota are connected to specific disease processes. Research on the topic needs to lead us to targeted specific microbes that can be adjusted. Since several pathways are used in the gut-brain axis connection, understanding this connection opens the door to treatments and interventions that will improve the quality of life for patients and their families. The gut microbiome is dynamic and influenced by diet, medication, stress, environment, and lifestyle. Innocuous manipulation of the microbiome with diet has little risk and amazing potential for benefits to holistic health.

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