



Microbiome and Mental Health, Specifically as It Relates to Adolescents

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Abstract

Purpose of Review This article reviews the relationship of the microbiome, the gut-brain axis, and depression. It also will review factors which can influence this relationship, such as chronic stress, medications, and the Western diet typically consumed by adolescents.

Recent Findings Changes in the gut microbiome increase the release of microbial lipopolysaccharides (LPS) which activate a gut inflammatory response. Gut pro-inflammatory cytokines stimulate the afferent vagal nerve which in turn impacts the hypothalamic-pituitary-adrenal (HPA) axis inducing symptoms associated with depression. Recent research suggests that gut inflammation can induce neuroinflammation which, in turn, stimulates microglia activation and the kynurenine pathway and can activate systemic inflammation-inducing depressive symptoms.

Summary Promoting a healthy diet and lifestyle changes, limiting exposure to pesticides, limiting medications that affect the microbiome and the use of such things pre/probiotics and other interventions may complement existing efforts to curb the rise in depression. Alternative and complementary therapies may serve as effective treatments in adolescents with depression.

Keywords Microbiome · Probiotics · Depression · Adolescents · Leaky gut · Diet · Autism · Anxiety, stress

Introduction

There has been an increasing rise in the incidence of depression in adolescents, by as much as 33% [1, 2]. This has coincided with a ninefold increase in the likelihood of suicidal ideation in adolescents [3]. The increase in suicide rates, especially among females, has increased by 65% since 2010 [1]. This alarming rise in depression and suicidality has highlighted the limits of available treatments. Several meta-analyses have shown that most antidepressants do not offer clear advantages over placebo for children and adolescents, with the exception of fluoxetine and escitalopram for depression in youth [4, 5].

Drastic lifestyle and cultural changes have likely contributed to the rise in the incidence of depression and suicidality. For

instance, both cross-sectional and longitudinal studies have found an association between the use of social media and depressive symptoms. Self-reported daily use of video games and internet exceeding 5 h was strongly associated with higher levels of depression and suicidality (ideation and attempts) in adolescents [6]. Increasing use of electronics has led to an increase in sedentary lifestyle and decreases in exercise, both associated with depression [7]. The internet has been used as another avenue for bullying. In one study, bullying which began at age 8 was associated with an increased later risk for suicide attempts and completed suicides [8]. In adolescents experiencing increased stress, there is emerging evidence that changes in the microbiome in the gut may increase the risk or severity of depression [9, 10]. Changes in the microbiome contribute to the production of pro-inflammatory cytokines that have been associated with psychiatric disorders [11–13].

In addition, other factors can change the balance of microbes in the gut (dysbiosis) leading to an increase in pro-inflammatory cytokines [14] and treatment-resistant depression [15]. The change in the American diet to processed foods, increases in sugar and sedentary lifestyle found in modern American adolescents, has been associated with weight gain, and obesity has been associated with a higher incidence of

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depression [16]. The relationship between obesity, inflammation in the gut, and the risk for depression is now receiving considerable attention. One study found that adolescents who were depressed had a 70% increased risk of being obese and obese adolescents had a 40% increased risk of being depressed [17]. An increase in the consumption of sugary soft drinks was significantly associated with greater weight gain and greater risk of obesity over time in children [18] and a 25-week randomized control trial (RCT) in adolescents found that a reduction in the intake of sugar-sweetened beverages had a beneficial effect on body weight that was strongly associated with baseline body mass index (BMI) [19]. One randomized controlled trial of a 12-week adjunctive dietary intervention for moderate to severe depression in adults demonstrated that dietary improvement may provide an efficacious and accessible treatment for depression [20].

This article will first review existing literature on significant changes in biological systems that can increase the risk of depression and then discuss alternative approaches that could prove to be effective and/or complementary interventions that are new on the horizon and may potentially reduce the risk for depression.

The Gut-Brain Axis

A number of groundbreaking articles have been written about the gut-brain axis which document the link between the production of pro-inflammatory cytokines in the gut, stimulation of the vagal nerve, and subsequent effects on the hypothalamic-pituitary axis (HPA) and inflammation in the brain that leads to psychiatric symptoms associated with depression [21••, 22••, 23••]. The changes in the normal population of microbes in the gut (dysbiosis) have been associated with many of the symptoms of depression [23••].

Seventy percent of microbes in the body are found in the human gut [24] and these bacteria contain 100 times the number of genes of the human genome [25]. The gut microbiota shapes intestinal immune responses during health and disease. As noted by Blaser in his seminal paper, “The Microbiome Revolution,” “It is reasonable to propose that the composition of the microbiome and its activities are involved in most, if not all, of the biological processes that constitute human health and disease” [26].

Gut-Brain Axis and Stress

Stress decreases *Lactobacillus* and *Bifidobacterium* and increases gram-negative bacteria leading to increases in lipopolysaccharides (LPS) [26]. LPS is recognized by Toll-like receptors on phagocytes and dendrites as foreign. These foreign antigens are presented to T lymphocytes, stimulating the

differentiation of T lymphocytes to Th 1 and Th 2 helper cells and the subsequent transcription of TNF kappa beta (β) to produce IL- β , IL-6, and TNF- α , all of which are pro-inflammatory (see Fig. 1). Not only will this stimulate the vagal nerve, but TNF- α also compromises mucosal integrity by promoting disintegration of tight junction proteins, like occludin, in the gut wall. Moreover, dysbiosis causes the disruption in short-chain fatty acids (SCFA), like butyrate, acetate, and propionate (neurohormonal-signaling molecules), which maintains gut integrity by maintaining tight junction proteins like occluding [9, 23••], hence the reason for the use of the term “leaky gut.”

The afferent loop of the vagal nerve is activated by the release of pro-inflammatory cytokines like tumor necrosis factor (TNF alpha), (IL)-1, and IL-6. The stimulation of the afferent nerve activates the HPA axis and corticotropin-releasing factor (CRF) is released. CRF stimulates the pituitary to release adrenocorticotropic hormone (ACTH). ACTH stimulates the adrenal gland to produce glucocorticoids and nor-adrenalin. Normally, once glucocorticoids are given off, a negative feedback loop occurs at the glucocorticoid receptors in the HPA and the HPA normalizes. In addition, the afferent loop of the vagal nerve stimulates the efferent vagal nerve. This increases acetylcholine (ACh) in the gut muscularis which stimulates the alpha 7 nicotinic ACh receptors of macrophages to decrease the release of IL-1 β , IL-18, and LPS. Thus, the feedback loop helps normalize the changes in the gut that initiated the inflammatory process [27••].

During chronic stress, the normal negative feedback loop becomes impaired. Circulating pro-inflammatory cytokines blocks the glucocorticoid receptor causing the HPA axis to become resistant to glucocorticoid stimulation [27••]. The release of CRF from the hypothalamus is further potentiated by the circulating pro-inflammatory cytokines resulting in

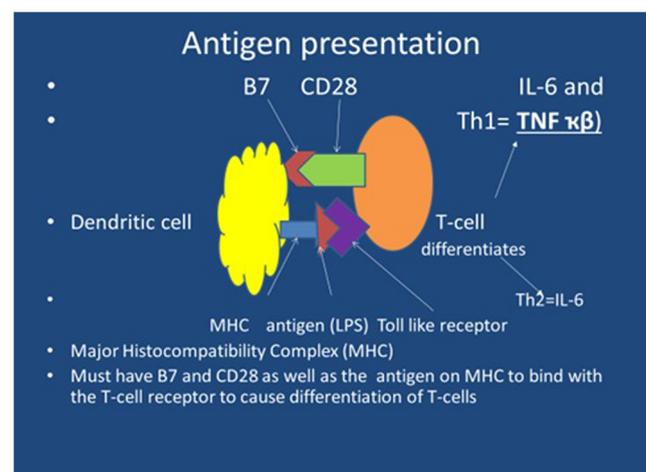


Fig. 1 LPS presents as an antigen on the major histocompatibility complex (MHC) to the Toll-like receptor of a T cell and the T cell differentiates to produce pro-inflammatory cytokines

sustained CRF activity. Hence, the HPA becomes hyperactive, a common finding in patients with depression. In addition, the release of CRF activates CRF 1 and CRF 2 receptors which activate mast cells to release TNF- α and proteases further increasing intestinal permeability. This process can be reversed using a CRF 1 and 2 receptor antagonist Astressin B and the mast cell stabilizer sodium cromolyn. Furthermore, anti-TNF- α -neutralizing antibody, protease inhibitors, and the neural blocker tetrodotoxin inhibited CRF-mediated intestinal barrier dysfunction in pigs [28]. The development of a CRF 1 antagonist is now being studied as a possible intervention for depression [29]. A systematic review of preclinical studies, examining the effects of probiotics on depressive symptoms, found that consumption of probiotics prevented stress-induced increases in ACTH, corticosterone, adrenaline, and noradrenaline suggesting attenuation of the HPA axis and subsequent decrease of depressive symptoms. [30]. Hence, there may be other adjunctive interventions that address the inflammation associated with depression.

A meta-analysis has also shown elevated levels of C-reactive protein (CRP), interleukin-1 (IL-1), and interleukin-6 (IL-6) in a study of depression in adult clinical and community samples [11]. Significantly higher levels of tumor necrosis factor- α (TNF- α) and IL-6 have been found in depressed patients as compared to controls [10] and blood levels of soluble interleukin-2 receptors, TNF- α , and IL-6 were higher in patients with major depressive disorder than in controls [31]. A recent study revealed that cerebral spinal fluid (CSF) CRP levels correlated with plasma CRF levels and these higher levels found in unmedicated depressed patients also correlated with CSF and plasma TNF alpha and IL-6 levels. Of note, the TNF levels correlated with decreased motivation and IL-6 levels correlated with anhedonia found in depression [32]. A similar study found that cytokines were associated with anhedonia in adolescents [33]. In addition, increased CRP has been associated with decreased connectivity between the ventral striatum and the ventromedial prefrontal cortex (vmPFC), which correlated with increased anhedonia and increased CRP predicted decreased dorsal striatum to vmPFC and pre-supplementary motor area connectivity. These findings correlated with decreased motor speed and increased psychomotor slowing. Finally, connectivity between the striatum and vmPFC was associated with increased plasma IL-6 and IL-1 beta. In addition, this study demonstrated that inflammation is associated with decreased functional connectivity within the corticostriatal reward circuitry in depression [34]. In conclusion, certain cytokines may be associated with specific symptoms of depression. High levels of cytokines, specifically IL-6, TNF- α , and CRP, have been found in depression [35]. A 2013 review summarizes several preclinical and clinical studies showing that microbiota stimulates immune challenges that influence anxiety and depressive-like behaviors [36].

The Role of the Vagal Nerve, Cytokines, and Stress on “Sickness Behavior” and Indoleamine 2,3-Dioxygenase in Depression

“Sickness behavior” (fatigue, decreased motivation, anhedonia, cognitive impairment, and sleep disruption) is associated with the activation of microglia in the brain. Microglia normally help in the pruning process in the brain. They can be activated by cytokines produced by macrophages and monocytes that cross blood-brain barrier, the afferent vagal nerve, increased levels of glutamate following acute stress exposure [37•] and increased LPS in the gut [38]. In turn, excess stimulation of microglia can lead to excess cytokines (IL-beta and TNF alpha) and Toll-like receptors (TLR4, TLR2, NLRP3, and P2XR7) which all lead to impaired synaptic plasticity. The result is neuronal dysfunction and mental health disorders with neurovegetative symptoms similar to depression [39].

Depressive states during inflammatory somatic disorders are also associated with increased pro-inflammatory cytokines and activation of indoleamine 2,3-dioxygenase (IDO). Activation of IDO and its subsequent enzyme kynurenine monooxygenase by pro-inflammatory cytokines diverts tryptophan from the production of serotonin towards the production kynurenine and the subsequent production of quinolinic acid, a strong agonist of the glutamatergic *N*-methyl-D-aspartate receptor [40•]. The disruption of the IDO pathway by inflammation has been linked to depression. Activation of IDO, as measured by the kynurenine to tryptophan (K/T) ratio, is associated with the severity of depressive symptoms. Higher K/T ratios were associated with a more severe depression [41•].

Hence, depression or depressive-type symptoms that occur when the normal microbial population is changed in the gut may not only be directly related to the effect of cytokines on the normal feedback loop of the vagal nerve but also may be influenced by inflammatory cytokines and their effect on microglia and the IDO pathway during stress (see Fig. 2).

Other Factors Associated with Changes in the Microbes in the Gut That Lead to Depression

Antibiotics and other medications, processed foods, sugar, glyphosate, pesticides, inflammatory bowel disease, and, as noted, obesity can also contribute to changes in microbes in the gut leading to depression.

Obesity, Diet, and Depression

Obesity is an increasing problem among American youth. The relationship between obesity, diet, and subsequent

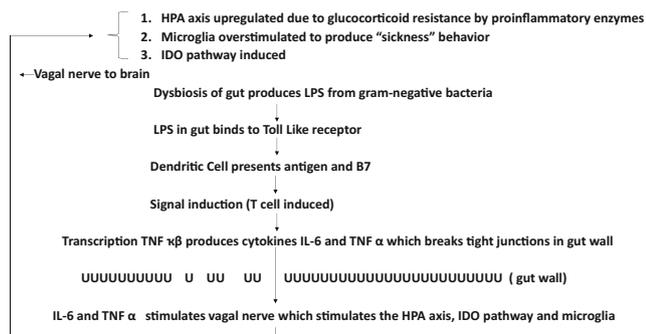


Fig. 2 Dysbiosis releases LPS from gram-bacteria to start a cascade of processes that leads to “leaky gut.” Inflammatory cytokines stimulate the vagal nerve and cause compromise of the blood-brain barrier to cause inflammation in the brain. The vagal nerve then stimulates the HPA axis to cause glucocorticoid resistance and over-reactivity found in depression. The vagal nerve and inflammation result in the overstimulation of microglia associated with symptoms associated with depression called “sickness behavior.” The inflammation in the brain also activates the IDO pathway decreasing the kynurenine to tryptophan (K/T) ratio associated with depression

inflammation in the gut and the risk for depression is now receiving considerable attention. There are a number of reasons for increased obesity and depression in adolescents, especially in females [15]. One study demonstrated that exposure to sexual and physical abuse during childhood increases the risk of severe obesity later in life [42]. In a meta-analysis, 26 studies that evaluated groups of ultra-processed foods (such as snacks, fast foods, junk foods, and convenience foods) or specific ultra-processed foods (soft drinks/sweetened beverages, sweets, chocolate, and ready-to-eat cereals) were selected. The results showed that most studies have found positive associations between consumption of ultra-processed food and body fat during childhood and adolescence [43].

High-fat fast food and processed food increase intestinal permeability and depression symptoms by causing dysbiosis [44]. Increases in fatty foods increase LPS across the gut wall [45] and increases in Toll-like receptors (TLR) that increase TNF alpha, IL-6, and other pro-inflammatory cytokines [46], all linked to an increased risk of depression. All of these factors contribute to the link between “leaky gut” and depression.

In addition, processed food and subsequent weight gain can also cause insulin resistance by signaling pro-inflammatory cytokines from adipose tissue [47]. Insulin resistance leads to carbohydrate craving, complicating the problems with obesity and may lead to diabetes. Depression has been found to be as twice as frequent in people with diabetes compared with those without diabetes [48]. One explanation for this may revolve around SCFAs. A decrease in the production of SCFA can affect satiety and can influence the development of obesity. SCFAs activate glucagon-like peptide 1 (GLP1) and peptide yy (PYY) in intestinal enteroendocrine L cells in

the ileum and colon. PYY reduces appetite by acting on neuropeptide Y (NPY) and GLP1 decreases appetite and stimulates insulin secretion [49, 50]. Therefore, lower levels of SCFAs ultimately prevent appetite suppression and carbohydrate craving may occur. In addition, other factors can influence craving. Chronic ingestion of a high-fat diet and sugar interferes with leptin and insulin signaling in the brain. Decreases in leptin can increase hunger which may lead to obesity, insulin resistance, and ultimately depression [51].

Addressing lifestyle adjunctive interventions that can lead to a healthier gut and a decrease in inflammation may decrease symptoms of depression and improve response to antidepressants. Other interventions that decrease inflammation may also be helpful. For instance, new research has shown that patients with treatment-resistant depression and inflammation may be identified by an increase in high-sensitivity C-reactive protein (hs CRP). Treatment of patients with a tumor necrosis factor (TNF) antagonist, infliximab, experienced a greater than 50% improvement in the Hamilton Scale for Depression (HAM-D) in 62% of treatment-resistant patients with depression as compared to a 33% in the placebo-treated group [52]. TNF alpha is a cytokine that has not only been implicated in treatment-resistant depression [53], which is produced when LPS increases, [10] but it plays a role in stimulating the vagal nerve when changes in the gut occur secondary to decreases in normal microbiome diversity [21•, 22•, 23•].

The link between the American diet and obesity is clearly linked to risk for depression and later diabetes. These factors require that we as clinicians look at the diet in our patients with depression, especially if it is refractory. Changes in diet may be important early interventions to reduce the risk of developing depression.

Sugar and Artificial Sweeteners

Sugar (including fructose) is an integral part of the adolescent experience. The recommended amount of sugar a person should eat per day by the American Heart Association is 5–8 g. Most Americans eat about 41 g per day. Eating too much sugar can cause an imbalance in the normal bacteria to yeast ratio (80%/20%) in the gut. Dysbiosis occurs and toxins given off by these yeasts can enter the bloodstream and cause inflammation and stimulate the vagal nerve.

Another complicating factor is that adolescents have resorted to using artificial sweeteners to reduce obesity. However, these have been linked to glucose intolerance [11, 54] and raise blood sugar by perhaps favoring the growth of bacteria that are associated with obesity-like Bacteroidetes and Firmicutes [55].

Alcohol

Experimentation with alcohol often occurs during adolescence. Emerging data suggests that alcohol-induced alterations of the microbiota may explain reward-seeking behaviors as well as anxiety, depression, and craving in withdrawal and increase the risk of developing psychiatric disorders [56]. One study demonstrated that some alcohol-dependent subjects developed gut “leakiness,” which was associated with higher scores of depression, anxiety, and alcohol craving after 3 weeks of abstinence. Moreover, subjects with increased gut permeability also had altered composition and activity of the gut microbiota [57], suggesting that addressing gut microbiota may be relevant in alcohol-dependent youth.

Sedentary Lifestyle and Lack of Sleep

A sedentary lifestyle has also been shown to lead to obesity [58] and lack of sleep can also contribute to obesity because sleep decreases glucose tolerance, decreases insulin sensitivity, increases ghrelin, and decreases leptin. The latter 2 increases appetite [47, 59]. Adolescent lifestyle changes with less exercise and sleep can become a troublesome component of increasing obesity, disrupting the gut, and increasing the risk for developing depression.

Inflammatory Bowel Disease

Adolescents with IBS may have an increased risk of depression [60]. Non-celiac gluten sensitivity (NCGS) has been associated with dysbiosis which may in turn causes gut inflammation, diarrhea, constipation, visceral hypersensitivity, abdominal pain, dysfunctional metabolic state, and peripheral immune and neuro-immune communication [61]. Whether NCGS is associated with depression remains to be determined. In regard to the association of gluten with other psychiatric disorders, there have been two case reports of hallucinations produced in children that disappeared once gluten was eliminated [62, 63].

Pesticides

Pesticides, insecticides, and herbicides are potent toxins, some with antibiotic activity. In a recent review of pesticides, depression, and suicide, a total of 11 studies on depression and 14 studies on suicide were reviewed. Of these reports, 4 reports found increased rates of suicide in areas with intensive pesticide use compared with those with lower use. Agriculture workers had higher risks for suicide compared with other workers in 4 studies. Thus, the evidence of associations between pesticide exposure and depression or suicide has been demonstrated in some populations. However, the available

studies used varied epidemiological approaches. Existing data is very limited and inconclusive [64]. For those affected by exposure, the risk for mental health sequelae from pesticides may be increased in carriers of genetic variants associated with reduced metabolism due to variations of expression of the cytochrome p450 enzyme 2D6 (the enzyme responsible for metabolizing pesticides). Slow metabolizers have been found to have higher levels of pesticides with evidence of oxidative stress and glutathione depletion [65, 66].

New research is beginning to investigate the link between the use of a widely used herbicide and “leaky gut.” This herbicide, which carries antibiotic activity, contains a substance known as glyphosate which prevents the conversion of fructose in wheat to phosphoenolpyruvate (PEP). PEP is converted into amino acids and neurotransmitters in the gut. This is known as the Shikimate process. The antibiotic effect kills normal gut microbes, particularly *Bifidobacterium* which is essential to the gut and breaking down wheat. Glyphosate also depletes methionine needed for the methylation of DNA and production of neurotransmitters and acts as a chelating agent to reduce minerals and downregulates the ability to use vitamin D. More research is needed to investigate whether the use of pesticides with glyphosate on foods, such as wheat, disrupts normal bacterial gut composition, contributing to the development of depression [67].

Oxidative Stress and Inflammation

TNF alpha and inflammation in the gut increase oxidative stress which produces reactive oxygen species (ROS). When mitochondria, which can normally neutralize ROS [68], become overwhelmed with increases in ROS (often seen in traumatic brain injury), damage to the mitochondria electron transport system occurs and this process has also been associated with depression and bipolar [69]. Reduced glutathione (GSH) is sacrificed by glutathione peroxidase to the oxidized disulfide form (GSSH) to neutralize ROS. During active mania, glutathione, an antioxidant, is decreased and lipid peroxidation increases (forming more ROS) [70]. This decrease in glutathione may be a compensatory effect towards increased oxidized stress during mania. In fact, in a DBPCT using 2000-mg *N*-acetylcysteine (NAC) in bipolar patients, there were large decreases in depressive symptoms as compared to a placebo group [71]. NAC is known to increase glutathione. NAC may be a useful adjunct in patients with depression. In addition, oxidative stress and glutamate transmission are disrupted in both depression and cannabis use disorder (CUD) and NAC normalizes glutamate transmission. NAC was effective at promoting abstinence among adolescents with CUD with heightened baseline depressive symptoms [72].

Medications

Single short-term antibiotic courses can disrupt the normal gut flora for months. When given in succession, particularly early in life, dysbiosis may become irreversible. Of course, in some of the most striking cases, antibiotic treatment allows the overgrowth of the pathogenic bacteria (e.g., *Clostridium difficile*), inducing potentially lethal conditions. However, non-antibiotic medications can also alter normal gut bacterial composition [73]. Antibiotics can change the gut flora but clinicians should also be aware that other medications can do the same. Proton pump inhibitors (PPI) and antipsychotic medications are associated with a decrease in diversity in the gut microbiome [74]. In addition, PPI has been linked to a decrease in Clotridiales and increase in Actinomycetales, Micrococcaceae, and Streptococcaceae, which are implicated in dysbiosis and increased susceptibility to *Clostridium difficile* infection. Bahr et al. (2015) demonstrated that shortly after risperidone use in children, a decreased ratio of Bacteroidetes: Firmicutes in the gut microbiome was associated with an increase in body mass index over time, resembling trends seen in obese patients [75]. A possible explanation for the weight gain is that primary bile acids (which are associated with weight gain) are normally converted into secondary bile acids by microbes in the gut. Risperidone changes the gut microbes and thus prevents the conversion of primary bile acids (known to be associated with weight gain) to secondary bile acids [76].

Thus, stress inflammatory bowel disease, antibiotics and other medications, processed foods, sugar, obesity, sedentary lifestyle, lack of sleep, glyphosate, and other pesticides may increase the risk for depression in adolescents by causing oxidized stress and changes in the normal microbial population and dysbiosis leading to “leaky gut.” Hence, it is important to determine if the increase in inflammatory cytokines and oxidative stress may be related to refractory depression. As noted previously, hs CRP elevation seen when inflammation is present and has been associated with treatment-resistant depression. Further proof of this association has been studied by Chamberlain et al. (2018) [77]. In this study, elevated hs CRP was found in treatment-resistant patients with depression but not in treatment-responsive patients with depression. More research is needed to determine which interventions can be used to decrease inflammation and oxidative stress.

The Role of Early Life Experiences That Can Increase the Risk of Depression in Adolescents by Causing Dysbiosis

Stressors during pregnancy can not only change microbes in the gut of the mother but can also increase inflammatory cytokines in the brain of the fetus and these inflammatory

cytokines can persist into adulthood [78]. Furthermore, specific early life events that may increase the risk for depression may be associated with the use of antibiotics in the first year of life [79]. Reduced gut microbial diversity by exposure to antibiotics in early infancy may lead to the production of pro-inflammatory cytokines by way of dysbiosis. The strength of these associations increased with the number of antibiotic courses, and with exposure at younger ages. Also, these associations differed by antibiotic class [80]. Recurrent antibiotic use has also been associated with depression and anxiety [73, 80].

Infants born by C-section may have lower Bifidobacterium [81] and pre-term infants lack Bifidobacterium and Lactobacillus [82]. The use of formula [83] and early introduction of solid food before 6 months of age may increase the risk for obesity [84]. A formula can increase insulin secretion and decrease leptin (responsible for fat consumption and controlling appetite) [83]. These factors along with the immaturity of the immune system and the gastrointestinal barrier may explain the peak prevalence of food allergies or food sensitivities (intolerance) at an early age [85] related to dysbiosis. Some evidence suggests that early use of antibiotics, C-sections, and absence of breastfeeding and the linkage to food allergies, obesity, and inflammation in the gut may be indicators of risk for depression in adolescents. Much more studies are needed.

Emerging literature suggests that early interventions which may change the course of dysbiosis may be helpful. It is interesting to note a small recently published prospective RCT where 75 infants, who were randomized to receive *Lactobacillus rhamnosus* or placebo during the first 6 months of life, were followed up for 13 years. Gut microbiota was assessed at the age of 3 weeks, 3, 6, 12, 18, 24 months, and 13 years of age. At the age of 13 years old, ADHD or autism (AS) was diagnosed in 6/35 (17.1%) children in the placebo and none in the probiotic group ($P=0.008$). The mean (SD) numbers of *Bifidobacterium* species bacteria in feces during the first 6 months of life were higher in the intervention group (9.12 (0.64) vs. 8.26 (1.24) log cells/g; $P=0.03$). While this sample size was very small, these preliminary data suggest that time-limited probiotic supplementation early in life may reduce the risk of neuropsychiatric disorder development later in adolescence [86]. In addition, probiotics fed to infants decreased intestinal permeability as measured by lactulose/mannitol ratio [87]. Only mannitol should be able to cross the gut barrier. When lactulose is seen in the urine, intestinal permeability is thought to be increased [87].

Therefore, taken together, early stressors, formula feeding, delivery by C-section, early exposure to antibiotics, and early exposure to processed foods may upset the normal population of the immature gut leading to “leaky gut” and a greater risk of developing obesity and depression during adolescence. Clinicians should include questions about these events during their developmental histories. Whether the application of probiotics and a healthy diet can prevent depression remains

to be seen. Further study is needed to determine if the use of these interventions should be considered earlier in life to potentially decrease the risk of depression in adolescents.

Application of Interventions During Adolescence That May Improve the Gut-Brain Axis and Decrease Depression

Given the role played by the vagal nerve in mediating the effect of the gut bacteria on the brain, it is quite conceivable that altering vagal nerve signaling, using vagal nerve stimulation (VNS), could counteract the effects of dysbiosis on the brain. In fact, during a 5-year open-label prospective study of patients with refractory depression, VNS was associated with a higher rate of first-time remission (43.0% vs. 25.7%) for treatment as usual, a higher cumulative response rate (67.5% vs. 40.9%), and a higher response rate in people who had not responded to ECT (59.6% vs. 34.1%). However, vagal nerve stimulation is somewhat invasive, requiring surgery and the placement of a device [88].

A meta-analysis and a systemic review of several studies completed on adults demonstrated that a subgroup analysis of studies conducted in healthy versus depressed individuals had significant improvements on the moods of individuals with mild to moderate depressive symptoms using probiotics. However, the studies were limited by the variety of probiotic dosing, bacterial strains, and strain combinations used [89, 90].

Several controlled studies have now begun to look at specific strains of probiotics in an attempt to determine which may be more effective in decreasing symptoms of depression. Messaoud and colleagues [91, 92] found probiotic formulations of *B. longum* and *L. helveticus* could improve anxiety and depression in all participants, and also in those who had lower urinary free cortisol levels at baseline. Steenberger [93] in a triple blind randomized controlled study demonstrated participants who received the 4-week multispecies probiotics intervention showed a significantly reduced overall cognitive reactivity to sad mood, which was largely accounted for by reduced rumination and aggressive thoughts as compared to those participants who received the placebo intervention. In a DBPCT, Akkeshah and colleagues [94] included 40 patients with a diagnosis of MDD based on DSM-IV criteria whose age ranged between 20 and 55 years. Significant beneficial effects were found on the Beck Depression Inventory, insulin homeostasis, insulin resistance, hs CRP concentrations, and glutathione concentrations, following the consumption of *Lactobacillus acidophilus* (2×10^9 CFU/g), *Lactobacillus casei* (2×10^9 CFU/g), and *Bifidobacterium bifidum* (2×10^9 CFU/g) for 8 weeks. This latter study is significant because it measured many factors which were previously discussed that is associated with depression. Treatment with probiotics has demonstrated some efficacy in reducing the hyperactivity

of the HPA axis in subgroups of depressed patients [95]. While these preliminary data are promising, more work is needed to characterize the specific strains, doses, formulation, and duration of treatment to optimize response which is lacking in these studies.

A recent pilot study has demonstrated that using up to 900 billion CFU twice a day of three strains of *Bifidobacterium*, four strains of *Lactobacillus*, and one strain of *Streptococcus thermophilus* for 8 weeks decreased anxiety in autistic children and youth and changed the microbes in the gut [96]. Another study correlated an increase in anxiety and aggression, an increase in stomach problems, and a decrease in verbal ability each time microbes changed in the stool of the autistic participants [97].

Probiotics have also been shown to have an impact upon weight gain. In one study, probiotic feeding during the early years and monitored for 10 years modulated the gut microbiota which in turn restrained excessive weight gain [98]. However, the use of probiotics with prebiotics (a type of fiber that nourishes healthy probiotics) seems to be even more beneficial. Prebiotics are the nutrition that probiotics thrive on. Prebiotics can lower LPS, increase SCFAs, and increase satiety peptides (thus decreasing hunger) which decreases metabolic parameters associated with obesity, especially if given early in life [99]. In addition, the administration of probiotics (*Lactobacilli* and *Bifidobacterium*) as live microorganisms or fermented products with prebiotics improved the body weight, abdominal fat, and intestinal barrier function [100].

Attention to diet which can improve microbial health in the gut is very important. Studies of western populations have shown that depression is higher in low socioeconomic areas where less probiotics and fermented foods are consumed [101]. Higher counts of *Bifidobacterium* species and *Lactobacilli* in fecal samples were found in rural Japanese individuals who maintained traditional high-fiber diets rich in fermented foods, vegetables, and fish as compared to urban Canadians who had high levels of *Clostridia* [102]. As noted, before, modern diets high in processed foods result in dysbiosis and high fat and sugar intake increase *Bacteroides* which have been associated with the production of LPS and gut permeability [103]. LPS which has also been shown to decrease antioxidant status and elevated oxidative stress, as noted previously, are found in patients with major depression [104]. Diets which include turmeric, soy, cocoa, green tea coffee, blueberries, pomegranate, and honey have high phytochemicals that act as antioxidants.

Changing diets to fermented foods (that contain probiotics) can increase the bioavailability of mood-regulating B vitamins, magnesium, and zinc. Since inadequate brain magnesium appears to reduce serotonin levels, and since antidepressants have been shown to have the action of raising brain magnesium, magnesium deficiency treatment or eating fermented foods that increase magnesium may be beneficial for depression [105]. In

regard to vitamin D₃, in currently depressed persons, 25(OH)D was inversely associated with symptom severity suggesting a dose-response gradient, and with a risk of having a depressive disorder at 2-year follow-up [106]. In a meta-analysis by Swardfagera et al. (2013) [107], 17 studies measured peripheral blood zinc concentrations in 1643 depressed and 804 control subjects. Zinc concentrations were approximately – 1.85 μmol/L lower in depressed subjects than in control subjects. Depression was associated with a lower concentration of zinc in peripheral blood.

Treating individuals with zinc, magnesium, and vitamin D₃ deficiency should be considered in depressed youth and blood levels should be monitored for zinc and magnesium when used.

As noted previously, the effect of pro-inflammatory cytokines on the normal feedback loop of the vagal nerve, the effect on microglia, and the effect on the IDO pathway caused by changes in the gut microbes can all lead to the development of depressive symptoms. Hence, reducing inflammation in the brain may reduce the severity of depression. Omega-3 fatty acids have long been known to increase anti-inflammatory cytokines. Omega-3 fatty acids have been correlated with decreases in depression and symptoms of mania in adolescents [108•]. Studies using omega-3 fatty acids on youth with depression have been promising. The OATS (*Omega-3 and Therapy Studies*) involved a 12-week RCT on 95 youth from ages 7–14 years of age. Seventy-two had depression and 23 had bipolar disorder. None had medication/psychotherapy in previous month except stable stimulants and sleeping aids. The study compared omega-3 fatty acid supplementation (Ω3), individual family psychoeducational psychotherapy (IF-PEP), and their combination in youth with subsyndromal bipolar disorders (bipolar disorder not otherwise specified [BP-NOS], cyclothymic disorder [CYC]). The combined treatment led to a decrease in depressive symptoms in BP-NOS/CYC and endogenously depressed youth, as well as a decrease in behavioral symptoms in depressed children. The omega-3 fatty acids decreased manic symptoms in BP-NOS/CYC youth and increased executive function in all youth. Some patients were on stimulants. Twenty patients, aged 6–17, had a diagnosis of bipolar disorder. The dose ranged from 1.3 to 4.3 g of Ω3 daily, with 85% taking ≥ 2.0 g/day. Manic symptoms decreased by 30% in 50% of the youth and by 50% in 35% of youth. Participants with more than 2.0 g/day improved more than those on less than 2 g/day [109•].

Conclusions

There remains clear evidence that some individuals with depression are refractory to medications and other interventions that are currently used for depression. Although modern life has in some ways made life more convenient, it may also be a

contributor to increased rates of depression, especially in adolescents. Increasingly, depression is linked to the changes in modern daily life stressors like chronic bullying, physical and sexual abuse, obesity, medications, pesticides, lack of sleep, diet, and sedentary lifestyle which have all been linked to the production of inflammatory cytokines and dysbiosis.

This review further highlights the biological changes resulting from perturbations in the gut microbiota including activation of the HPA axis and cytokine production leading to inflammation. As presented in this review, a growing body of evidence supports the important role of the microbiome in physical and mental health and our potential to develop interventions that support healthier development.

Early interventions such as the use of probiotics and prebiotics, organically grown foods, fermented foods, and omega-3 fatty acids and treating deficiencies of vitamin D, magnesium, and zinc can be helpful.

This review also highlights the opportunities for the prevention of mental health conditions among youth and that focused research can allow us to harvest these opportunities. Addressing the stress of chronic abuse and bullying can be preventive. Adding interventions like meditation may also be useful, changing dietary habits during adolescence by eliminating processed foods, sugar, and artificial sweeteners; increasing exercise; normalizing sleep; and reducing alcohol and internet use.

Although the research is in its infancy, there seems to be strong evidence that the gut-brain axis may play a crucial role in the pathogenesis of many psychiatric conditions, including adolescent depression. Much more research is needed.

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Compliance with Ethical Standards

Conflict of Interest The author declares that she has no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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