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The Role of Nutrition and the Gut-Brain Axis in Psychiatry: A Review of the Literature

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Abstract
Introduction: Individuals suffering from psychiatric disorders experience high levels of illness burden and a significantly reduced quality of life. Despite targeted psychopharmacological strategies and complementary psychotherapeutic procedures only moderate effects are obtained, and the risk of relapse is high in many patients. Worldwide, psychiatric diseases such as depression are continuously increasing, challenging the personal life of the affected as well as their families, but also whole societies by increasing disability, early retirement and hospitalization. According to current scientific knowledge psychiatric disorders are caused by a multifactorial pathogenesis, including genetics, inflammation and neurotransmitter imbalance; furthermore, also lifestyle-associated factors gain rising importance. In line with this, there is growing evidence that the gut microbiota and nutrition have an impact on the onset and course of psychiatric disorders. ***Aim:*** This narrative review highlights the important role of nutrition in psychiatric care and underlines the significance of nutritional advice in the multifactorial, biopsychosocial treatment of patients. It focuses on current dietary interventions such as the Mediterranean diet, dietary supplements and modifications of the gut microbiota with pre-, pro- and postbiotics. ***Results:*** Recent studies support the connection between the quality of diet, gut microbiota and mental health through regulation of metabolic functions, anti-inflammatory and antiapoptotic properties and the support of neurogenesis. Dietary coaching to improve mental health seems to be an additional, cost-effective, practical, nonpharmacological intervention for individuals with psychiatric disorders. ***Conclusion:*** The use of nutritional interventions in psychiatry equips therapists with a promising tool for both the prevention and treatment of psychiatric disorders. Besides pharmacological therapy, psychotherapy and physical activity, nutritional interventions are an important pillar in the multifactorial, biopsychosocial treatment of psychiatric disease and could be used as a potential therapeutic target.

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Introduction

Estimations based on epidemiological data suggest that psychiatric disorders will dramatically increase in the years to come [1]. Psychiatric disorders, and especially depression and anxiety disorders, form a major component of the global burden of disease [2]. Despite intensive efforts to improve mental health treatment, 15–30% of depressive patients exhibit therapy resistance to current state-of-the-art treatments [3]. Only one third of patients with depression reach complete remission with psychopharmacological therapy. For severe depression, combination therapies of antidepressants and psychotherapy are usually recommended [3], with only moderate effects. Typically, many of the prescribed drugs cause unwanted side effects, leading approximately 50% of psychiatric patients to prematurely discontinue their psychopharmacological treatment [4]. Hence, additional therapeutic strategies that are easy to implement in everyday life and that can be obtained over a long period of time are urgently warranted.

Driven by rapid urbanization, our lifestyle and food changed drastically in the last decades: traditional lifestyles (including social community structures, physical activity and diet) changed in a relatively short period of time. These changes are related to the high prevalence of depression and other psychiatric disorders in western, urbanized countries [5]. In line with this, diet and nutrition are viewed as an important factor contributing to the pathogenesis of somatic as well as psychiatric disorders [6]. As inhabitants of the western urbanized countries, we see ourselves confronted with the following paradox: despite the nearly unlimited availability of food, we often favor nutrient-poor, energy-dense, genetically modified and processed food. As a result, many of us are overfed and undernourished. Even though the calorie counts are rising, we do not meet the nutritional recommendations [7].

In particular, we are often deficient in nutrients which are crucial for brain function such as vitamins of the B complex (vitamin B_1 and pantothenic acid), folate, magnesium and zinc [7, 8]. According to Austrian data, more than half of all women (52.2%) and 43.2% of men are below the recommended intake of vitamin B_1. The average intake of folate lies below the recommended dosage of 300 μg/day for both men and women in all age groups with only 27% of women and 42% of men lying within the normal range of the recommended intake [7]. Further, fiber-rich vegetables and whole grains are less eaten than it would be recommended [7, 9]. This has also recently been confirmed by the Austrian national nutritional report: only 14% of Austrians reached the recommended intake of fiber (30 g/day), with an average intake of 20.1 g/day in women and 21.7 g in men being clearly below recommendations [7].

The exact mechanisms of how diet affects mental health are currently widely investigated. However, there is no doubt that our brain, having a high energy turnover, relies on a continuous, nutritive energy supply (including amino acids, lipids, vitamins, minerals and trace elements) obtained from our diet [5, 10]. A traditional diet with whole foods including vegetables, fruit, seafood, fish, wholegrains, lean meat and nuts is a good prevention of a number of diseases [11]. Our dietary habits modulate gut bacteria, the immune system and circuits of inflammation which are known to be involved in the pathogenesis of psychiatric disorders such as depression [10, 12]. Neurotrophic factors such as the brain-derived neurotrophic factor (BDNF) are essential for neuronal plasticity and are also modified by dietary factors [13, 14].

The aim of this review article is to further underline the important role of nutrition in psychiatric care [15], to emphasize the need of an extended biopsychosocial treatment strategy which includes nutritional interventions as for the prevention and treatment of psychiatric disorders and to strengthen the emerging discipline of *nutritional psychiatry* [5, 15].

"Mind Moves Matter!" – or Vice Versa? Dietary Interventions

In the last few years, the number of studies which aimed to depict a connection between the quality of our diet and mental health was rapidly increasing. For example, a high-quality diet was connected to lower rates of depression and lower suicidal risk [16, 17].

Already very early in our lives, nutrition has a major impact on mental health with serious nutritional deficiencies contributing to the pathogenesis of depressive and psychotic disorders [18–20].

Further, patients suffering from schizophrenia often exhibit a poor diet, especially when in a symptomatic episode. Adding to this, the consumption of a western diet (mainly characterized by a high intake of saturated fat and refined sugar accompanied by a low consumption of fiber and fruit [21]) is also related to the commonly poor financial situation of schizophrenic patients [22] leading to the high prevalence of metabolic syndrome and cardiovascular events [23]. Peet [24] demonstrated in a study of the ecological analysis of schizophrenia and diet that an increased consumption of refined sugar results in a de-

creased state of mind for schizophrenic patients with poor social functioning and a higher number of days spent in hospital. However, to date, according to a Cochrane review on dietary advice for patients with schizophrenia, interventional studies are sparse, and more research is needed to determine whether dietary advice has an effect [25].

Early modifications of diet seem crucial for the prevention of psychiatric disease. In this context, the PREDIMED trial is of high importance because it showed that a Mediterranean style diet with nuts led to a reduced risk for developing depression [26]. The Mediterranean diet (also often called a Cretan diet) is a form of diet inspired by the Mediterranean countries. Studies of the last few years showed that this kind of diet not only leads to a lower incidence of cardiovascular disorders, but also to a better mental health status [27]. A classical Mediterranean diet consists of the following main ingredients: vegetables, fruit, nuts, legumes, fish and unsaturated fatty acids [28]. A recent review showed that the adherence to a high-quality diet, such as a Mediterranean style diet, was connected to a lower risk for depression with a linear dose-response relationship [12]. Nevertheless, if a Mediterranean style diet is disassembled into its individual components, there is no single ingredient which accounts for its positive effects alone. It appears as though the complex characteristics of the nutritional composition are the basis for its efficacy [29].

Beside the recommendation for a Mediterranean-based diet, there are different studies focusing on nutritional interventions in psychiatric disorders to date to deepen the knowledge about the connection between nutrition and mental health. For example, Stahl et al. [30] showed that a dietary coaching could prevent elderly persons to develop symptoms of depression. Importantly, this nutritional intervention was as effective as psychotherapeutic treatment. The participants of this study, which received dietary coaching over a time period of 6 weeks, experienced a 40–50% reduction of depressive symptoms and a higher quality of life. These effects even persisted over 2 further years [30]. Similar changes were also observed by Jacka et al. [31], who compared the effects of dietary advice to a social support group. The group receiving dietary advice scored significantly lower on the MADRS scale after 12 weeks compared to the social support group. Moreover, 32.3% of individuals in the dietary group achieved remission (MADRS score <10) [31]. Likewise, an Italian study showed effects of nutritional psychoeducation in patients with affective disorders and psychosis. In comparison to state-of-the-art psychoeducation the dietary intervention group showed significant improvements of symptom severity, sleep quality and Mediterranean diet adherence [32]. According to the mentioned publications, dietary advice to improve mental health seems to be a cost-effective, practical, nonpharmacological intervention for patients suffering from depression.

The expenditure of time for dietary coaching was comparable to short-time psychotherapy: Stahl et al. [30] implied 6–8 sessions of dietary advice over a 6- to 12-week period with semiannual booster sessions (3, 9 and 15 months after the treatment phase). While the first session lasted 1 h, the subsequent sessions lasted 30 min each [30]. In the study of Jacka et al. [31], participants took part in 7 individual dietary support sessions of approximately 60 min (4 sessions weekly and 3 sessions every 2 weeks). The dietary coaching study of Bersani et al. [32] comprised 5 weekly group sessions (in groups of 8 patients) which lasted 90 min each.

Another diet which has been recommended since the 1920 is the ketogenic diet which is a controlled high-fat, low-protein and low-carbohydrate diet usually with a 4:1 lipid:nonlipid ratio (fat to protein and carbohydrate ratio) [33]. In animal models, a ketogenic diet improved anxiety-related behaviors, depression-like behavior, autism-spectrum disorder-related and schizophrenia-related behavior, actions, which might be partly attributable to alterations of the gut microbiota [34, 35]. However, these studies have a limited generalizability to human conditions. To date, studies in patients are lacking and inconclusive. Therefore, there is no sufficient evidence for the use of a ketogenic diet in mental disorders [36].

Summing up, evidence to date indicates that a Mediterranean style diet is advisable for patients with mental disorders [31, 32]. Further, easy memorable concepts to increase vegetable and fruit intake (such as "eat the rainbow" [37], thus advising the patient to add differently colored fruit and vegetables to every meal) could be used within this concept.

Dietary Supplements

Special nutrient supplements such as ω–3, S-adenosyl methionine (SAMe), N-acetylcysteine, zinc, B vitamins and vitamin D have been widely investigated. A number of studies supports the efficacy of ω–3 fatty acids in the treatment of affective disorders, posttraumatic stress disorder, Alzheimer's disease and in the prevention of psychosis [38]. Further, there is evidence for the preventive effect of ω–3 fatty acids in cardiovascular disorders. In 2004, a low ω–3 index (defined as the sum of eicosapen-

taenoic acid [EPA] and docosahexaenoic acid [DHA] in relation to the total amount of fatty acids) was identified as a risk factor for sudden cardiac death, and the level of >8% was set as a target value for high cardiovascular risk [39]. However, to date there are no target values set for psychiatric disorders.

ω–3 fatty acids have the following main mechanisms of action: they modulate neurotransmitters through reuptake inhibition, synthesis and receptor binding, support neurogenesis by enhancing BDNF and have anti-inflammatory and antiapoptotic effects [38, 40]. Current research focuses on members of the ω–3 family, namely DHA and EPA, which are predominantly found in fish. A meta-analysis of case-control studies revealed a lower EPA and DHA status compared to a healthy control group in depressed patients [41]. Supplementation with ω–3 fatty acids improved symptoms of depressed patients, especially in those with a high inflammatory status [42]. Epidemiological data demonstrate that ω–3 fatty acids can effectively treat depression, and ω–3 fatty acid consumption (containing 1.5–2 g of EPA per day) has mood-stimulating effects in depressed patients [43, 44]. In schizophrenia, fatty acid supplementation showed positive effects; however, data are limited by small sample sizes, short study duration and insufficient characterization of patients [45].

Some clinical studies have shown that SAMe, being responsible for the methylation of neurotransmitters, is an effective antidepressant and demonstrates augmentative effects in antidepressant therapy [46]. L-Methylfolate serves as an important intermediate molecule for the conversion of folic acid to SAMe. Further, SAMe has a positive effect on neuronal membrane fluidity [47]. When SAMe was coadministered with escitalopram in depression, it showed increased antidepressant effects, but only in male patients [48]. The Cochrane review on the use of SAMe concluded that high-quality studies are lacking und underlines the need for more investigations [49].

Furthermore, N-acetylcysteine, an amino acid-based component, modulates glutamate and is a potent anti-inflammatory antioxidant with neuroprotective effects. It had effects in bipolar affective disorder, schizophrenia, impulse control disorders and addictions [50].

Interestingly, also zinc deficiency can trigger depressive symptoms, and supplementation with zinc was shown to improve depressive mood, especially as add-on therapy to antidepressants [51]. The exact reasons why a zinc deficiency syndrome could lead to symptoms of depression are not entirely identified yet; however, there are several hypotheses. Zinc is an essential trace element involved in cytokine modulation and hippocampal neurogenesis via BDNF and modifies N-methyl-D-aspartate (NMDA) and glutamate activity [51]. It is involved in cellular immune response, hormone regulation and regulation of the hypothalamic-pituitary-adrenal axis. A zinc deficiency could therefore lead to depressive symptoms via activation of inflammatory processes [52] and modification of the NMDA receptor [53].

Not unexpectedly, also B vitamins are essential for our nervous function. Especially a vitamin B_9 (folic acid) deficiency has been repeatedly found in depressed patients [54]. Interestingly, low folate levels caused depressed patients to respond less to antidepressant treatment, indicated a higher probability of relapse and worsen cognitive performance [54, 55], while an adequate intake had protective effects [56].

In addition, the hype around vitamin D in different areas of somatic medicine had also reached psychiatry some years ago. Vitamin D_3 is found in food of animal origin, on the other hand it is endogenously produced by exposure to sunlight (UVB radiation). A high intake of vitamin D (predominantly found in fish) is a particular characteristic of the Mediterranean diet. Vitamin D deficiency was found in many mental disorders, such as depression and attention deficit hyperactivity disorder [57–59]. A meta-analysis by Spedding [60] revealed significant effect sizes for vitamin D substitution in depressed patients. In a double-blind, placebo-controlled trial of Krivoy et al. [61], vitamin D supplementation was associated with a trend towards improved cognition in patients with schizophrenia but did not affect psychosis, mood or metabolic status. Despite the low vitamin D serum levels often found in mental disorders, data are still inconclusive, and more randomized clinical trials should be performed [62].

Nevertheless, despite some effects of dietary supplements on mental health and well-being, a combination of micronutrients and macronutrients that fits the body's natural physiological needs and represents the full range of nutrients in whole foods may be more effective than a supplementation with isolated nutrients alone [63].

Gut Microbiome and the Gut-Brain Axis – The Bacteria in Our Gut and Their Importance to (Mental) Health

If a microbial community inhabits a certain habitat, it is called microbiota. Microbiota reside both on the outer and inner surfaces of our body (such as the skin, the oral cavity, the genitourinary tract and the gastrointestinal tract). Every bacterium contains genetic material. The to-

tality of all genes and genomes found in the microbiota are called "microbiome" [64]. Nowadays, there are fast and cost-effective methods of DNA sequencing to reveal the individual composition of the microbiome [65]. The composition of the gut microbiome varies with age, gender and environmental factors (such as birth mode, breastfeeding, medication, hygiene, toxins), geographical origin, disease and diet [66–69].

Between the intestine and the brain there is a bidirectional communication pathway called the gut-brain axis, which connects the enteric nervous system to the central nervous system [70]. Hence, the intestinal microbiota and diet play an important role in this gut-brain interaction system, which was shown to be involved in the pathogenesis of psychiatric disorders [71]. For instance, a reduction in the number of bacterial species has been reported in a range of mental disorders as well as obesity [72, 73].

From a psychiatric perspective, it is interesting that intestinal bacteria intervene directly in our neurotransmitter metabolism, especially in the serotonin metabolism. In preclinical murine studies, it was shown that probiotics based on changes in serotonin metabolism might have an antidepressant and anxiolytic effect [74]. In particular, *Lactobacillus plantarum* showed antidepressant efficacy in mouse models [75, 76].

Secondly, a damaged intestinal flora (*"dysbiosis"*) contributes to an increased permeability of the intestinal mucosa (*"leaky gut"*), which leads to an increased immune response and chronic neuroinflammation, a major cause of mental illness [77, 78]. This inflammatory response could in turn stimulate cytokine production, which occurs when bacterial components (such as lipopolysaccharides from the bacterial cell wall) bind on circulating macrophages and monocytes [79]. Cytokines, soluble intercellular signaling molecules, are produced in the brain and in the periphery and are involved in the pathophysiology of mental disorders such as depression and anxiety disorders [80, 81] as they influence neurotransmitter synthesis, release and reuptake [82]. Recently, cytokine blockers have also been discussed as a future psychopharmacological target [83, 84].

Psychosocial stressors, poor nutritional quality and the metabolic syndrome contribute to chronic inflammation and should subsequently be the focus of our treatment and prevention strategies for mental disorders as modifiable risk factors [85–87]. Dietary approaches could alter gut bacteria and gut bacterial metabolites such as short chain fatty acids, decrease cytokine production, lower overall inflammation and enhance the effect of current psychopharmacological approaches.

Pre-, Pro- and Postbiotics

In order to positively influence the composition of the intestinal microbiota, prebiotics, probiotics and postbiotics are used. Prebiotics consist of nondigestible nutritional components that may favor the growth of intestinal bacteria [88]. Examples of prebiotics would be complex carbohydrates, fructans and glucans which could affect the intestinal microbiome [89].

Probiotics are living, reproducible microorganisms, which were first described in 1907 by Elie Metchnikoff [90]. In studies *Lactobacilli* and *Bifidobacteria* are widely used [91, 92]. In healthy adults, there was also a significant reduction in stress and anxiety after a probiotic treatment with *Lactobacillus* and *Bifidobacterium* [93]. Studies using probiotics to treat depression show some contradictory results [94–96]. In the pilot study by Bambling et al. [95], which investigated the use of probiotics in depressive patients, there were significant improvements in depressive symptoms during supplementation, which, however, ceased after discontinuation of the probiotics after 8 weeks and under antidepressive monotherapy. For schizophrenia, studies did not show improvements in symptoms when patients were treated with adjunctive probiotics, but improvements of gastrointestinal function and immune response [97–99].

The effects of psychopharmacological treatment on the microbiome have not been widely studied so far, but there are indications that these may exert antibiotic properties and thus have lasting effects on the gut microbiome [100–102].

Postbiotics are bacterial soluble factors and components of the bacterial cell wall. Initial studies suggest a positive effect on inflammatory markers by postbiotics [103]. However, to date, there are no interventional studies for postbiotics in psychiatric disorders.

All in all, several double-blind, placebo-controlled interventional studies with a sufficient case number will be required in order to prove the effects of pro-, pre- and postbiotics on mental illness.

Outlook

Multifactorial diseases need multifactorial approaches. It would be conceivable that future psychiatrists and psychotherapists prescribe special diets to address the specific nutritional deficiencies of mentally ill patients, balance the gut microbiota, reduce chronic inflammation

and to optimize the effects of pharmacological and psychotherapeutic treatment.

In the last few years, the number of studies on nutrition and mental diseases, a specialty which has been considerably neglected for a long time, has risen; however, more research on special dietary advice for patients is needed.

Changes in the food industry and rapid globalization have brought lasting changes to traditional diets. Supplements, prebiotics and probiotics are often used in everyday life by both mentally ill persons and healthy people. However, since dietary supplements are not subjected to pharmaceutical efficacy trials, more rigorous, double-blind, placebo-controlled trials are needed to test their effectiveness.

The same applies to special diets such as the Mediterranean style diet. It may also be important to have an individualized approach that determines the diet form and additional supplement(s) needed, their application and duration of the treatment. These approaches need to be adapted to the individual special circumstances of the patient.

Lastly, the results of this research should be integrated into cross-curricular trainings and included in public health programs. A concern of our group is to draw attention to this important topic in the education of medical students and to integrate this essential area in compulsory psychiatric education. A first step in this direction has already been taken with an elective course which will be offered for the first time in the summer term of 2018 at the Medical University of Graz. We are one of the first European universities to teach future psychiatrists in nutrition. In our inpatient group therapy sessions for depressive patients at the Medical University of Graz, patients are informed about the basics of a Mediterranean diet by means of easily memorable concepts (e.g., "eat the rainbow" [37]).

Conclusion

An adequate supply of micronutrients and macronutrients is essential to well-being and provides the foundation for microbiome health, low inflammation and also for the efficacy of other psychotherapeutic and psychopharmacological interventions.

Therefore, basic nutritional knowledge is essential for psychiatrists and psychotherapists. Lifestyle interventions such as dietary coaching could be used as promising, cost-effective and practical intervention for people with mental illness. Nutritional interventions should be integrated as an important pillar in the multifactorial, biopsychosocial treatment of our patients.

Disclosure Statement

All authors declare that there are no conflicts of interest.

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