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Nutrition in the Treatment of Schizophrenia: Rationale and Review of Recent Evidence

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Abstract

Purpose of Review This review aims to provide an overview of the pathophysiological basis for the use of nutritional strategies in the treatment of schizophrenia, outline the evidence for dietary intervention strategies, and discuss clinical considerations around their implementation.

Recent Findings Inflammatory and metabolic mechanisms underlying the pathophysiology of schizophrenia are well-characterized and may provide promising treatment targets. Existing literature on dietary intervention strategies for schizophrenia provides evidence supporting the use of antiinflammatory diets, select vitamins and supplements, and more targeted approaches such as gluten-free or ketogenic diets in specific subsets of patients. Implementation of these strategies is limited by physician education on nutrition, inherent difficulties in researching nutrition, patient factors, and structural factors.

Summary Nutritional approaches represent an important and potentially underutilized treatment strategy to reduce symptoms and improve quality of life for patients with schizophrenia.

Keywords Schizophrenia · Nutrition · Supplements · Inflammation · Microbiome · Metabolism

Introduction

There has been increasing interest in the role of nutrition in treating psychiatric disorders; however, a reliable evidence base has only recently begun to emerge. Theories about metabolic, immune, and inflammatory etiologies of mental illness provide a basis from which to infer that diet impacts mental health, but human nutrition research is largely comprised of cross-sectional population-based studies, and studies on controlled dietary interventions are methodologically difficult to conduct [1]. Furthermore, physicians receive little formal education on nutrition during their medical training [2]. Within psychiatry, non-pharmacological interventions such as psychotherapy and lifestyle changes are employed, but medication remains a mainstay of treatment. This is especially true in cases of severe mental illness, where long-term psychotropic medication may indeed be necessary, but not sufficient to relieve suffering.

The role of inflammation and metabolic aberrancies in the pathophysiology of schizophrenia is well-characterized, and emerging evidence suggests that dietary interventions may aid not only in counteracting the metabolic effects of antipsychotics and improving general health [3], but also in treating the symptoms of schizophrenia itself. Nutritional strategies may be a useful adjunct to medication in the treatment of schizophrenia and could target symptoms not fully addressed by medication, reduce medication burden, and improve quality of life and functioning. This review will provide an overview of the pathophysiological basis for the role of nutrition in treating schizophrenia, summarize current evidence on dietary intervention strategies, and discuss barriers to their implementation with proposed solutions.

Role of Nutrition and Metabolism in the Pathophysiology of Schizophrenia

A comprehensive review of the links between dietary factors and schizophrenia is beyond the scope of this paper, but several major areas are discussed below to provide background supporting the use of dietary interventions.

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Inflammatory and Metabolic Pathophysiology

Schizophrenia has been associated with elevated levels of cytokines and other inflammatory blood markers, likely due to an interaction between predisposing genetic or prenatal factors and environmental insults, such as infection or psychosocial stress. Early stressors can activate and prime the immune system, including microglial immune cells in the central nervous system (CNS), to maintain a chronically inflamed state and react more robustly to later insults [4]. Several inflammatory markers have been demonstrated to have dose-dependent relationships with schizophrenia symptoms and, in both the general population and people with schizophrenia, increased inflammation has been associated with cognitive impairments [5]. Premorbid inflammatory processes also contribute to the metabolic aberrancies observed in schizophrenia, which are compounded by antipsychotic medications, inflammatory and obesogenic dietary patterns, and other lifestyle factors [6]. Impaired glucose metabolism is observed even prior to the initiation of antipsychotic treatment in schizophrenia [7]. Insulin resistance has been linked to impaired regulation of synaptic plasticity and alterations in dopamine, glutamate, and GABA release [8], all of which may play roles in the pathophysiology of schizophrenia. Polymorphisms in the mitochondrial genome and impaired mitochondrial function are also thought to be factors in the pathogenesis of schizophrenia and may lead to altered neuronal activity, impaired synaptic plasticity, and increased oxidative stress, further driving inflammation [9]. Essentially, common inflammatory and metabolic mechanisms may underlie both the psychopathology of schizophrenia itself and associated metabolic pathology, suggesting that dietary interventions improving metabolic outcomes have the potential to treat primary schizophrenia symptomatology as well.

Gluten Sensitivity

Epidemiological studies dating back to the 1940s have linked wheat consumption to schizophrenia [10], and while there is an epidemiological link between Celiac disease and schizophrenia, non-Celiac gluten sensitivity (NCGS) is also thought to be implicated in a subset of patients with schizophrenia [11]. NCGS is characterized by gastrointestinal and/or extraintestinal, including neuropsychiatric, symptoms induced by the ingestion of gluten-containing foods in those without Celiac disease [12]. While it remains a clinical diagnosis, immunoglobulin G (IgG) antibodies to gliadin, a protein found in gluten, are present in a subset of people with NCGS [13]. Antigliadin IgG antibodies are found in about one-third of people with schizophrenia, at a higher rate than in the general population [14], and are associated with elevated inflammatory markers in that population [15], suggesting that a subset of those with schizophrenia may have inflammatory pathology related to gluten sensitivity.

Gut Microbiome

The gut-brain axis represents a bidirectional communication network between the gastrointestinal tract and the CNS. The gut microbiome is one component of this system and consists of microorganisms living within the digestive tract that communicate with the brain via primarily neuroendocrine and neuroimmune mechanisms. Gut microbiota can also produce neuroactive molecules such as serotonin or dopamine [16]. Decreased microbiome diversity and increased intestinal permeability are linked to inflammatory immune processes and have been associated with symptomatology and cognitive impairments observed in schizophrenia [17]. Environmental factors, including diet, appear to play a much larger role than genetics in shaping the human microbiome [18], and therefore have potential treatment implications.

Vitamins and Omega-3 Fatty Acids

Low maternal vitamin D levels during prenatal development have been associated with an increased risk of schizophrenia in offspring [19]. In patients with schizophrenia, lower vitamin D levels have been associated with increased severity of negative symptoms and cognitive deficits [20], and in first-episode psychosis patients, higher baseline vitamin D levels have been associated with lower positive and negative symptom scores 1 year after initial presentation [21]. Vitamin D plays a role in calcium homeostasis and affects the balance between gamma-amino-butyric acid (GABA) and glutamate, the brain's primary inhibitory and excitatory neurotransmitters, respectively, thereby affecting downstream cellular signaling [22]. Lower levels of folate and vitamin B_{12}, dietary factors crucial for proper neurodevelopment and neurological functioning, have also been described in populations with schizophrenia. This may be related to genetic polymorphisms involved in their absorption and metabolism, dietary insufficiency, or a combination thereof [19]. Omega-3 fatty acids have also received attention in relation to psychopathology, given that the brain contains a greater percentage of lipids than any other organ in the body, and docosahexaenoic acid (DHA), the most abundant omega-3 fatty acid, is essential for proper neurodevelopment and later neural functioning. However, evidence on serum and brain omega-3 fatty acid levels in schizophrenia has been mixed, with studies showing higher, lower, and comparable levels

in schizophrenia patients compared to healthy controls [23]. Abnormalities in levels of other vitamins, nutrients, and elements have been discussed in relation to schizophrenia as well, but have been less studied [19].

Evidence for Dietary Interventions in Schizophrenia

This section will review recent evidence on the effects of specific dietary interventions in humans on the positive, negative, and cognitive symptoms of schizophrenia, with a brief review of selected supplements. It is important to note that schizophrenia is a heterogeneous syndrome, with varying clinical presentations and multifactorial etiologies. Therefore, no one treatment works for all those diagnosed with schizophrenia and it is important to remember that interventions targeting inflammatory or other mechanisms outlined above may work in some subsets of people diagnosed with schizophrenia and not others. Characterizing the different phenotypes of schizophrenia so that we can better target effective treatment is an ongoing area of research.

General Considerations

Many studies assessing the use of diet in the treatment of schizophrenia have consisted of general nutrition education programs advocating for healthier eating in combination with other lifestyle interventions, like exercise. Such studies have demonstrated reduced psychiatric symptoms or improved quality of life in response to interventions, but the impact of diet was confounded by other variables and the dietary interventions used were non-specific [24]. It has also been suggested that reducing generally dietary inflammation may be beneficial, given the inflammatory pathophysiological processes in schizophrenia. This might involve reducing the consumption of pro-inflammatory foods, such as saturated fats, refined carbohydrates, and sugars, while increasing the consumption of nutrients with antiinflammatory properties such as omega-3 fatty acids, folic acid, and vitamins A, B, C, and D [25]. In one randomized controlled trial of 83 patients with schizophrenia and metabolic syndrome, half of the patients were assigned to a reduced-calorie Mediterranean diet emphasizing the consumption of fruits, vegetables, and foods rich in fatty acids and the elimination of sweets. The patients in the Mediterranean demonstrated improvement in several cognitive measures, whereas the control group without dietary intervention did not [26]. General good nutrition and antiinflammatory diets have been linked to prevention and improvement in a number of psychiatric disorders [27], but we will now turn to several more targeted dietary interventions, also summarized in Table 1.

Ketogenic Diet

The ketogenic diet was initially developed to treat treatment-refractory juvenile epilepsy and has since been explored as a treatment for several other neurologic and psychiatric conditions. It involves the consumption of high levels of dietary fat and very low levels of carbohydrates. This induces a metabolic change in which the body primarily utilizes fat and ketone bodies for fuel, as opposed to glucose. Several neurological diseases involve cerebral glucose hypometabolism, which is also observed in schizophrenia; thus, it is hypothesized the ketogenic diet may be metabolically favorable for brain function in schizophrenia. There is also evidence that it can reduce oxidative stress and inflammation

Table 1 Dietary and supplement treatment strategies for schizophrenia

Diet/supplement	Purported mechanisms	Potential clinical benefits
Ketogenic diet	• Reduce oxidative stress and inflammation [28] • Compensate for impaired cerebral glucose metabolism [28]	• Reduction of positive and negative symptoms [29–33] • Possible benefits to metabolic or gastrointestinal health [29, 30]
Gluten-free diet	• Avoid inflammatory reactions to gluten-containing foods in patients with non-Celiac gluten sensitivity and elevated antigliadin IgG antibodies [11–15]	• Reduction of positive and negative symptoms [34–36] • Improvements in cognition [35] • Possible reduction of other gluten-related symptoms, such as gastrointestinal problems
Probiotics and prebiotics	• Improve microbiome composition and diversity [16–18]	• Reduction of positive and negative symptoms [38–40] • Improvements in cognition [42, 43] • Reduction of gastrointestinal symptoms [41]
Omega-3 fatty acids	• Support proper neurodevelopment and neural functioning, particularly cell membranes [23] • Reduce inflammation [23]	• Reduction of positive and negative symptoms [45, 46] • Reduced depression and anxiety [48, 60] • Improvements in cognition [58, 59]
Vitamin D	• Modulate GABA/glutamate balance [22] • Maintain proper calcium homeostasis [22]	• Reduction of positive and negative symptoms [40, 63
B vitamins	• Support proper neurodevelopment [19] • Support neurotransmitter formation [19]	• Prevention of cognitive decline [64] • Improvements in cognition [64]

and animal studies suggest it may address GABA/glutamate imbalances seen in schizophrenia [28]. While evidence on the use of the ketogenic diet in schizophrenia from human studies is limited, there are some compelling results. Implementation of a ketogenic diet for 15 days in an opposite-sex pair of twins with schizophrenia resulted in decreased Positive and Negative Symptom Scale (PANSS) scores in both, with the male patient's score dropping from 82 to 75 and the female patient's score dropping from 97 to 91. Although these are modest changes in symptom scores, both patients still saw reductions in general psychopathology despite less-than-perfect adherence to the diet. Their scores returned to baseline 2 weeks after discontinuing the diet, but both maintained reduced body mass indices as compared to baseline [29]. In a case series describing two patients with schizophrenia diagnoses and chronic, treatment-refractory psychotic symptoms, both started a ketogenic diet for non-psychiatric reasons (weight loss and gastrointestinal problems, respectively), but experienced complete remission of their psychiatric symptoms on the diet and were able to discontinue antipsychotics [30]. Another case report described a patient with refractory hallucinations on antipsychotic treatment whose symptoms resolved within 3 weeks of starting a ketogenic diet without any change in medication and remained remitted for the next year on the diet [31]. A case series on two patients with schizoaffective disorder and treatment-refractory psychotic symptoms also described the resolution of psychotic symptoms on a ketogenic diet, with relapse of symptoms occurring shortly after lapses in the diet [32]. In a retrospective analysis of 31 inpatients with severe mental illness poorly controlled on medication, adherence to a ketogenic diet among the 10 who had schizoaffective disorder resulted in a mean PANSS score improvement from 91.4 to 49.3 ($p<0.001$) [33•]. As discussed earlier, it may be that use of a particular diet is effective only in a certain subset of people with schizophrenia who have some sort of shared pathophysiological mechanism. At this time, there are no randomized controlled trials evaluating the ketogenic diet as a treatment for schizophrenia, but it remains a promising area of research.

Gluten-Free Diet

As mentioned above, there is a subset of individuals with schizophrenia with elevated antigliadin IgG antibodies and associated inflammation who may be more sensitive to the effects of gluten [15]. An early pilot study trialing a gluten-free diet in schizophrenia included two patients, one positive for antitissue transglutaminase antibodies indicating Celiac disease, and one positive for antigliadin antibodies, suggesting NCGS. Both participants saw improvement in symptomology as measured by the Brief Psychiatric Rating Scale (BPRS) and Scale for the Assessment of Negative Symptoms (SANS), as well as improvement in extrapyramidal side effects [34]. A later randomized controlled trial included 16 patients with schizophrenia and schizoaffective disorders who were positive for antigliadin IgG and completed a 5-week inpatient intervention in which they were randomized to a gluten-free or gluten-containing diet. Fourteen patients completed the study and those on the gluten-free diet showed improvements on the Clinical Global Impressions scale and in negative symptoms as compared to those on a diet containing gluten [35]. A recent case report on a 55-year-old male with treatment-refractory schizophrenia and elevated antigliadin IgG also showed symptom improvement as measured by the PANSS after 2 weeks on a gluten-restricted diet, though the patient was unable to adhere to the diet beyond then and his symptoms returned [36]. Further research and larger studies are needed, but the use of a gluten-free diet may be an important component of treatment for a subset of people with schizophrenia spectrum disorders.

Probiotics and Prebiotics

The microbiome has been another area of interest as a potential treatment target in schizophrenia through the use of probiotics and prebiotics. Probiotics are live microorganisms that colonize the gut and may have beneficial health effects. They are found naturally in fermented foods such as yogurt and sauerkraut, or can be ingested in supplement form. Prebiotics are substances that foster the growth of helpful microorganisms and inhibit the growth of harmful microorganisms in the digestive tract, overall promoting a more favorable microbiome composition. They can be used in supplement form or are found naturally in foods containing nondigestible fiber such as oats, certain vegetables, and other plant foods [37]. The majority of research on microbiome-related interventions in schizophrenia thus far has focused on the use of probiotic or prebiotic supplements. In an open-label single-arm study, 29 outpatients with schizophrenia given 4 weeks of adjunct probiotic treatment saw significant improvement in anxiety and depression symptoms as measured with the PANSS, though it was noted that due to lack of a control group, the placebo effect could not be ruled out [38]. A double-blind placebo-controlled trial of 42 inpatients with schizophrenia treated with risperidone showed that half of the sample receiving adjuvant probiotic therapy had a greater reduction in symptoms as measured by the PANSS [39], and a double-blind placebo-controlled trial of 60 patients with chronic schizophrenia showed that treatment with high dose vitamin D plus probiotics for 12 weeks yielded significant improvements in PANSS scores as compared to placebo [40]. Another double-blind placebo-controlled trial of 65 outpatients with schizophrenia found that patients receiving adjunctive probiotic treatment showed

no significant differences in PANSS scores as compared to those receiving placebo, but did have fewer gastrointestinal symptoms [41]. A small study on the use of prebiotics in five participants with treatment-resistant schizophrenia on clozapine showed a decrease in positive and hostility symptoms as measured by the BPRS, as well as improvements in cognitive domains [42•], while a double-blind placebo-controlled study of 39 outpatients with psychosis on stable antipsychotic medication demonstrated significant improvement in cognitive scores as measured by the Brief Assessment of Cognition in Schizophrenia (BACS) with prebiotic use [43]. At least one study examined the use of dietary modulation to increase prebiotic and probiotic intake. In a 6-month randomized clinical trial including 50 individuals with schizophrenia spectrum disorders, a control group received regular conventional dietary advice while the intervention group was educated to increase prebiotic and probiotic intake through the incorporation of more dairy, fermented foods, leafy greens, fruits, and whole grains. Forty-four participants completed the trial and the intervention group showed significantly improved nutritional intake and more favorable metabolic profiles, but the study did not examine psychiatric symptoms as an outcome [44].

Omega-3 Fatty Acids and Other Supplements

Omega-3 fatty acids have been examined in both first-episode patients with schizophrenia and more chronic patients. In the former, younger population, this dietary strategy has been shown to be effective in several studies [45]. First-episode patients treated with omega-3 fatty acids in one study fared better than chronic patients [46]. Another study of 69 first-episode patients reported no overall advantage from omega-3 supplementation at the end of the 12-week study period, but did find an acceleration of treatment response time with omega-3 treatment [47]. In a study of 71 first-episode patients over 24 weeks of treatment with antipsychotics and either 1.32 g/day eicosapentaenoate (EPA) plus 0.88g/day of DHA or placebo, patients receiving the omega-3 fatty acids showed significantly better improvement on PANSS total score, depressive symptoms, and the general symptoms subscale, but not on the positive or negative subscales [48]. Others have tried to prevent the conversion to schizophrenia with omega 3 fatty acids in clinically high-risk patients [49], but the subsequent larger NEURAPRO [50] and NAPLS studies [51] did not find any beneficial effect. Results in chronic patients are more mixed with a few studies finding positive omega-3 effects [46, 52, 53] and some with no or worse effect compared to placebo [54–57].

Newer studies have also shown mixed results, suggesting differential responses to omega-3 fatty acids based on baseline metabolic state or phenotype. In patients with schizophrenia and metabolic syndrome on long-term olanzapine therapy, adding omega-3 fatty acids enhanced delayed recall [58•]. Another study looked at the effects of administering ethyl-EPA and vitamins E plus C either separately or together in patients with acute schizophrenia and differing baseline levels of red blood cell polyunsaturated fats (PUFAs). In patients with low baseline PUFAs, ethyl-EPA given alone impaired sustained attention, whereas in patients with high baseline PUFAs, vitamins E plus C given without ethyl-EPA impaired sustained attention. When ethyl-EPA and vitamins E plus C were given together in both baseline PUFA groups, however, neutral or slightly beneficial effects on attention were observed, possibly attributable to an antioxidant effect from the combined therapy [59]. A study on omega-3 adjuvant treatment with risperidone showed improved anxiety and depression symptoms in patients with recent onset psychosis treated with omega-3 fatty acids, but only in the subgroup of participants who had not received concomitant lorazepam during the 16-week study period [60]. Treatment with fish oil has also been studied for its effect on violent behaviors and hostility in schizophrenia, but showed limited to no effects [61, 62].

While a comprehensive review of the role of supplements in treating schizophrenia is beyond the scope of this paper, several other supplements discussed earlier have been studied for this purpose. For example, vitamin D in conjunction with probiotics was shown to decrease PANSS scores [40] and vitamin D replacement in patients with low levels led to improved scores on clinical assessments of both positive and negative symptoms [63•]. A randomized placebo-controlled trial of 120 first-episode psychosis patients found that those randomized to an adjunctive B-vitamin supplement containing folic acid, B_{12}, and B_6 or placebo for 12 weeks did not see improvement in overall symptomatology or global neurocognition. However, results did suggest that B vitamins had neuroprotective properties in select cognitive domains and that they improved subdomains of neurocognition specifically in female or affective psychosis patients [64]. L-methylfolate, the reduced, bioactive form of folate, was also found to improve PANSS scores compared to placebo in a 12-week randomized trial [65].

Implementation of Dietary Treatment Strategies

It is becoming increasingly clear that diet plays an important role in mental health and that incorporation of nutrition principles into the treatment of schizophrenia could benefit many individuals. Many patients are overweight or obese and proper nutrition and diet early in treatment could improve long-term metabolic abnormalities and prevent early mortality. Patients should consider attempting to implement choices with higher fiber and lower fat as their diets typically consist of more fat

and less fiber. While weight management was beyond the scope of this particular review, it is important to note that behavioral interventions and dietary interventions may not only improve psychiatric symptoms but metabolic outcomes as well. Notably, however, not all dietary interventions will contribute to weight loss. For example, gluten-free diets are typically not associated with a decrease in body weight and should not be mistaken as weight loss strategies.

Patients with treatment-refractory disease or with particular phenotypes of schizophrenia may benefit psychiatrically from targeted dietary interventions, such as gluten-free or ketogenic diets, but more research in these areas is needed. Better education of physicians on the role of nutrition in mental health is also crucial. However, even in areas of medicine where the role of diet has been better established, such as in metabolic and cardiovascular disease, dietary interventions remain difficult to implement. This section will address some of the barriers to their implementations and discuss potential solutions, depicted in Fig. 1.

Barriers to Dietary Interventions

On an individual level, motivation, feelings of self-efficacy, and attitudes towards dietary interventions can impact the ability to adhere to them, as can competing priorities in multiple areas of life, including work, relationships, or other health challenges. Social and environmental factors play a major role in dietary choices [66], which may be of particular relevance in the USA, where unhealthy foods are readily available and heavily advertised. People with severe mental illnesses such as schizophrenia often have increased difficulties with motivation and cognition, as well as increased hunger as a side effect of antipsychotic treatment, making it even more difficult to maintain healthy diets [67]. The availability of healthy food is also heavily impacted by socioeconomic factors [68, 69]. This may disproportionately affect individuals with severe mental illness, as it has been associated with lower socioeconomic status [70–72]. Finally, medical training on lifestyle interventions is limited and physicians' abilities to implement them are restricted both by time constraints and reimbursement models [73]. Some clinicians may also assume patients will be unwilling or unable to adhere to dietary changes, but anecdotally, many patients are very interested in learning about non-pharmacological approaches to improve their health and deserve education from their treatment providers about these options.

Potential Solutions

While increased education and awareness of nutritional interventions among psychiatrists are certainly needed, implementation will remain challenging in settings where appointment times are limited. However, psychiatrists and other mental health professionals may already be skilled in

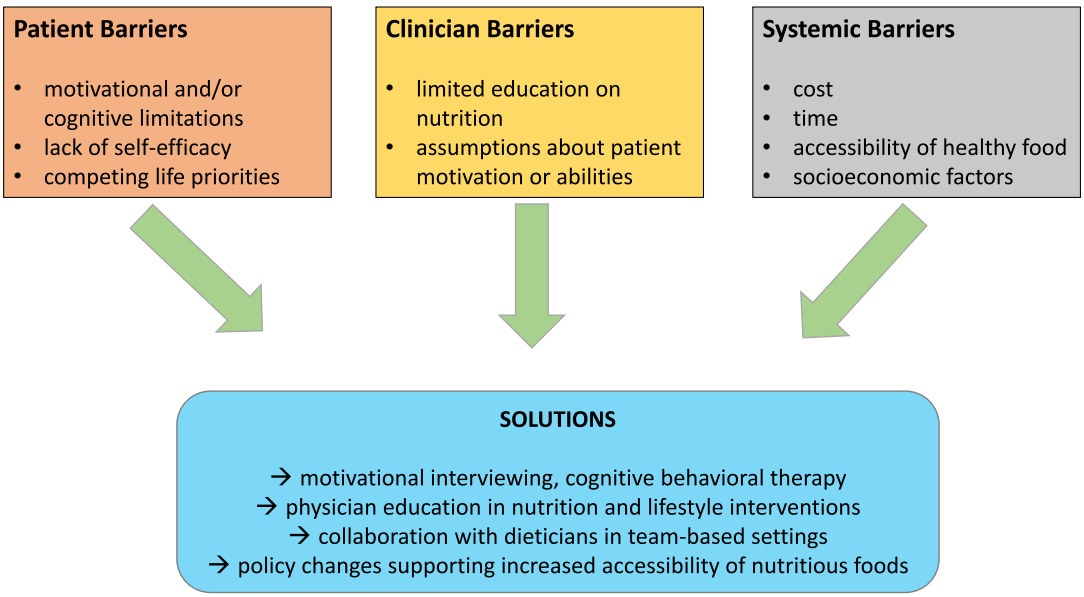

Fig. 1 Barriers to implementation of nutritional treatment strategies and potential solutions

the use of motivational interviewing, cognitive behavioral therapy, and other techniques that can be readily applied to counseling patients on dietary changes [74, 75]. In team-based settings, the incorporation of dieticians knowledgeable about mental health could be of great benefit [67, 76, 77]. Policies that support accessibility to healthy foods and other systems-level solutions will also be important, though more difficult to achieve in the short term.

Conclusion

We have a responsibility to offer our patients a full range of treatment options to improve their quality of life, particularly in the case of severe, chronic disease. For patients with schizophrenia, who suffer increased morbidity and mortality due to metabolic disease in addition to their psychiatric symptoms, the incorporation of nutritional approaches is of even greater importance. It is also imperative that we offer complementary and alternative treatment approaches, including nutritional, to *all* psychiatric patients in order to optimize recovery and reduce harm.

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Data Availability Not applicable.

Compliance with Ethical Standards

Ethical Approval All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki Declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

Competing Interests Dr. Deanna L. Kelly has served on advisory boards for Alkermes, Janssen, and Teva.

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- • Of importance
- •• Of major importance

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