

Addressing the gastrointestinal health associated with schizophrenia: The argument for a new nutrition-based intervention

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Abstract

The purpose of this paper is to review the literature linking schizophrenia with chronic inflammation and gluten sensitivity. In addition, the paper discusses the need for dietary interventions that may improve multiple health outcomes for patients. Individuals with schizophrenia are at much greater risk for the development of additional autoimmune disorders. Second generation anti-psychotic medications are the most effective treatment for schizophrenia, but there are numerous potential side effects to the medications. More specifically, individuals with schizophrenia who are treated with SGAs are at increased risk for obesity, diabetes, as well as elevated lipids and blood pressure. An effective evidence-based dietary intervention has the potential to improve numerous outcomes for individuals with schizophrenia.

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Addressing the gastrointestinal health associated with schizophrenia

Schizophrenia is one of the most severe forms of mental illness. According to the National Institutes of Health about 1.1% of the US adult population has schizophrenia. The costs to the disease are considerable, totaling \$63 billion a year in direct treatment, societal and family costs (1). Much of the cost (70%) comes in the form of indirect costs including lost work time for patients and care givers, social services and criminal justice resources (1).

There have been numerous potential causes of schizophrenia discussed in the literature. Several studies have addressed the possible importance of gastrointestinal health in the development of schizophrenia. For example, the role of the gut-brain axis in schizophrenia has been examined (2) as has the link between gastrointestinal disorders and schizophrenia (3). The link between the gut and brain is generated by the fact that nearly 70% of the immune system is clustered around the digestive tract. Autoantibodies that react against the body lead to autoimmune diseases, and can also lead to psychiatric conditions when able to cross the blood-brain barrier. The blood-brain barrier normally protects the brain but can become compromised due to chronic inflammation (4). Thus, what we eat, and more precisely foods we eat that cause inflammation, may result in an immune response within the body. While an immune response can be productive when fighting a cold or virus, an immune response can also cause significant problems within the body when it leads to autoimmune disease.

The concept of schizophrenia having an autoimmune component has been increasingly discussed (e.g., 5) and it has been suggested that the autoimmune response may play a causal role in the development of schizophrenia (6, 7). Consistent with this argument a meta-analysis found a significant association between schizophrenia and elevated levels of inflammation (8)

and the presence of antibodies (9). As a result schizophrenia has also been associated with a number of other autoimmune conditions. For example, a prior autoimmune disease raised the risk of developing schizophrenia by 29% (4) to 45% (10). Nine different autoimmune conditions were more common among individuals with schizophrenia than among controls including celiac disease, interstitial cystitis, Grave's disease, and polymyalgia rheumatica (10).

While schizophrenia is a complex disorder with many potential causes the literature suggests a link between autoimmune disease and schizophrenia. As a result, treatment should involve an effort to address schizophrenia as a potential autoimmune disorder. One mechanism for addressing autoimmune disorders is through diet and nutrition. The purpose of this paper is to discuss some of the literature linking schizophrenia with autoimmune disease and nutrition, and propose a nutritional intervention to address the numerous health problems associated with schizophrenia. While this is not the first paper to address this issue, the goal is to provide a discussion accessible to a general audience as well as practitioners and to encourage additional research into the role of nutrition in mental health treatment. Continued work is needed because prior interventions have often focused on weight loss, have tested questionable diets, or have involved small sample sizes. Design of an intervention that effectively reduces the health consequences of schizophrenia and antipsychotic medications would improve the quality of life for the many people living with this chronic disease.

Diet and mental illness

The link between nutrition and mental illness has not been a major focus in research. The lack of attention is noteworthy given that the brain relies on nutrients to function properly. Proper intake of certain nutrients can potentially avoid the onset of certain psychiatric symptoms or alleviate symptoms after

onset. For example, antioxidants, omega 3 fatty acids, and B Vitamins play an important role in cognitive function (11). Women had a reduced risk of psychosis with increased fish, omega 3 fatty acids, and vitamin D consumption (12). Recent research has begun to take a closer look at the role of diet and nutrition in specific mental illnesses. As mentioned above, the link between nutrition, gastrointestinal health, and schizophrenia has received increased attention (2, 3, 13).

The potential importance of effective nutrition is also motivated by the fact that the primary treatment for schizophrenia, second generation antipsychotic (SGA) medications, has numerous potential side effects. More specifically, individuals with schizophrenia treated with SGAs are at increased risk for obesity, diabetes, as well as elevated lipids and blood pressure compared to controls comprised of drug naïve patients or the general population (14-17).

Due to the numerous negative health effects, interventions have been designed to improve health outcomes (primarily weight) for individuals with schizophrenia. For example, psycho educational and cognitive behavioral approaches have been tested repeatedly with positive but small effects on weight (18). Interventions that rely on prescription medications to reduce antipsychotic related weight gain have also had only modest effects (19). Weight loss should not be the only health goal, and programs that focus on weight loss may or may not improve other health markers. For example, reductions in weight were not accompanied by improvements in fasting glucose or lipid profiles (20). Recent efforts to test the Dietary Approaches to Stop Hypertension (DASH) diet in overweight individuals taking antipsychotic medications resulted in weight loss and lower fasting glucose levels, but relatively modest effects on psychiatric symptoms and other health markers (21).

Efforts to assess the diets of people with schizophrenia have found diets comparable to the

general population (e.g., 22). However, given the substantial number of overweight and obese people in the general population, equivalence to the general population is not necessarily a desirable goal. In addition, most people in the population are not suffering from autoimmune conditions. Thus, given the adverse consequences of the disease and given the greater risk for negative health effects faced by individuals treated with antipsychotic medications it would seem the goal is a diet superior to the general population.

Numerous factors should influence a dietary and nutritional intervention. The correlation between schizophrenia and inflammation, the presence of antibodies, and the development of other autoimmune diseases suggests that steps be taken to reduce the autoimmune response. The autoimmune response can be triggered by a number of factors including diet. Below we discuss the literature that addresses the role of specific nutrients, as well as a number of abnormalities, several related to the autoimmune response, often encountered in individuals with schizophrenia.

Omega-3 fatty acids

Research has examined the role of polyunsaturated fats in psychosis. Two polyunsaturated fats are emphasized in the literature; the essential fatty acids omega-3 and omega-6. Omega-6 (n-6) fatty acids are pro-inflammatory while Omega-3 (n-3) fatty acids are anti-inflammatory. A number of sources indicate humans evolved eating a diet with a n-6:n-3 ratio of 1, but the current standard American diet (SAD) has a ratio of approximately 16:1 (23). Thus, the ratio has become highly skewed towards omega-6 fatty acid consumption. A higher ratio has been linked to greater risk for many diseases including inflammatory and autoimmune conditions.

Studies have found that individuals diagnosed with schizophrenia have decreased levels of fatty acids

(24), and it has been argued that there is adequate evidence for supplementation with omega-3 fatty acids for newly diagnosed psychosis (25). Omega-3 fatty acids may reduce side effects from AP medications due to their anti-inflammatory nature, and have a low risk of harm. While supplementation is one way to increase omega-3 intake, diet can also be used to increase omega-3 consumption. Just as importantly, dietary modifications can reduce omega-6 consumption. For example, industrial seed oils such as safflower, sunflower, and vegetable oils have high levels of omega-6 fatty acids.

Glutamate

The NMDA (N-methyl-D-aspartate) receptor is a glutamate receptor that is associated with psychotic symptoms. A relationship has been found between schizophrenia and anti-NMDA receptor antibodies (26). Among acutely ill patients admitted to an inpatient facility, 9.9% of the (unmedicated) patients with schizophrenia had anti-NMDA receptor antibodies compared to 0.4% of controls. It is yet to be determined whether patients identified with anti-NMDA receptor antibodies would benefit from an autoimmune-based treatment and maintained using an autoimmune dietary plan.

Vitamins and specific supplements

Numerous studies have assessed the value of supplementing with specific vitamins and other nutrients. The first, N-acetylcysteine (NAC), has value because it can increase glutathione, an important antioxidant found to be lacking in individuals with schizophrenia (27). Supplementation with NAC led to an improvement in general and negative symptoms, but not positive symptoms (28). The second, melatonin, is another antioxidant that plays an important role in the sleep-wake cycle. Individuals with schizophrenia often report insomnia and have suppressed levels of melatonin

(29). Supplementation with melatonin was found to improve sleep quality among individuals with schizophrenia (30), and may be preferable to prescription medications due to side effects and dependency concerns with common prescription options. Third, a number of studies have assessed vitamins B, C, D, and E. However the overall results have been mixed (13), and suggest that supplementation may be beneficial for some people. These vitamins are typically available in common multivitamins and represent a low cost intervention.

Food sensitivities

Autoimmune disease can be triggered by food sensitivities (31). Food sensitivities, particularly gluten sensitivity, has been associated with numerous diseases (32). Gluten contains gliadins (monomeric proteins) that promote intestinal permeability (i.e., leaky gut syndrome). Since the immune system is grouped around the digestive tract, gut permeability generates an autoimmune response that has been associated with numerous diseases.

The association between gluten sensitivity and schizophrenia has been known for decades (33). More recent research has also found an association between celiac disease and schizophrenia (34). Twenty-three percent of schizophrenia patients in the CATIE trials had moderate to high sensitivity to gluten compared to 3% in a comparison group (9). Elevated anti-gliadin antibodies, a marker for gluten sensitivity, were found among individuals with schizophrenia (35). Several serum biomarkers of gluten sensitivity were also elevated among people with schizophrenia, but that the immune response differed from that in non-schizophrenic individuals with celiac disease (36). Finally, several small studies found positive effects from placing individuals with schizophrenia on a gluten-free diet (34, 37).

While the subject of less research, individuals

with schizophrenia have been found to exhibit greater sensitivity to casein, the protein in dairy foods, before (Niebuhr et al, 2011) and after (39) diagnosis. Thus, there appears to be considerable evidence that individuals with schizophrenia have greater food sensitivities. Severance, Yolken, & Eaton (3) provide a thorough discussion of how food sensitivities can lead to immune activation and contribute to the development of schizophrenia. Additional research is needed to confirm a causal link between food sensitivity and schizophrenia.

Insulin resistance

Insulin resistance occurs when muscle and fat cells in the body do not respond properly to insulin, and thus do not absorb glucose from the bloodstream. High carbohydrate diets common in the United States play a role in the development of insulin resistance (40). Insulin resistance can also result from an autoimmune response against insulin receptors (41), and leads to higher blood glucose levels and increases the risk of developing type 2 diabetes. Individuals newly diagnosed with schizophrenia have increased insulin resistance compared to controls (42). Because people in the study were newly diagnosed with schizophrenia and had little to no exposure to antipsychotic medications, insulin resistance could not be attributed to the AP medications. Thus, while the higher rates of diabetes are often linked to the metabolic effects of antipsychotics, individuals newly diagnosed with schizophrenia may already be at risk for developing diabetes.

A nutritional intervention

Individuals with schizophrenia are more likely to have a number of health problems, some related to autoimmune disease, and some the result of the treatment for schizophrenia. Regardless of the mechanism it is crucial to develop and test interventions designed to reduce and potentially eliminate some of these health problems. For example, individuals with

schizophrenia are more likely to have chronic inflammation and are at-risk for autoimmune disease. While there is debate about whether the relationship between inflammation and schizophrenia is causal or merely correlational (43), there remain important reasons to reduce chronic inflammation. If there is a causal relationship for some people, then nutritional interventions may play a role in treating people with schizophrenia. If the relationship is correlational, then nutritional interventions may still reduce the health consequences associated with elevated levels of inflammation. Consequently, there may be benefit to nutrient dense diet that promotes overall health.

While a dietary intervention should be individualized to meet the needs of the patient, there are several principles that should guide the intervention. First, the diet has to be a lifestyle diet and not a temporary weight loss diet. Schizophrenia is a chronic disease and a potential diet must be a long-term eating plan to achieve long-term weight maintenance and improved health outcomes. Second, the diet should focus on food quality in order to promote overall health. Diets that include heavily processed foods such as pre-packaged meals found in the grocery store, while potentially leading to weight loss, are unlikely to provide overall health benefits. One diet that meets most of the criteria and is the subject of considerable research on the Mediterranean diet.

The Mediterranean diet (MedDi) is commonly promoted for beneficial effects on health, including a number of health problems found in individuals with schizophrenia. The typical MedDi focuses on whole grains, lean meats, fish, vegetables, legumes, nuts, fruit, olive oil, and moderate amounts of dairy. Observational and interventional studies have assessed the effect of the MedDi on weight management, and the risk of diabetes, cardiovascular disease, and inflammation. For example, the MedDi has been associated with improved glycemic control and insulin sensitivity (44). In addition,

the MedDi has been associated with reductions in coronary heart disease (45) and stroke (46). A meta-analysis of RCTs found that MedDi adherence was associated with statistically significant reduction in weight (47). However, studies have found mixed results regarding the relationship between a MedDi and the development of inflammation. Some research has found individuals whose diet was more consistent with the MedDi had lower C-reactive protein (CRP) levels in the blood (48), but others have found no significant effect on CRP (49).

The Mediterranean diet has many characteristics consistent with current knowledge on a healthy diet, and its adoption would likely have positive health effects. However, an emphasis on carbohydrates (grains) is questionable for some individuals with schizophrenia, particularly the substantial segment with autoimmune disease as evidenced by gluten sensitivities, insulin resistance, diabetes, or other elevated inflammatory markers. The link between grain intake (particularly gluten containing grains) and inflammation would suggest that many individuals with schizophrenia would benefit from a grain-free gluten-free diet. In addition, the high proportion of people with insulin resistance or diabetes would benefit from a lower carbohydrate diet. While the MedDi is associated with improved glycemic control, the comparison is typically with a standard American diet high in refined carbohydrate. Such comparisons do not determine whether a diet *without* grains would improve inflammatory markers relative to whole (or refined) grains. Individuals on a gluten-free diet have superior glucose control when compared to the MedDi (50). Thus, based on the substantial research base a dietary intervention will benefit from following the principals of the MedDi. However, the intervention must be adapted to take into account the specific needs of each patient.

While a modified Mediterranean diet is a viable alternative, there are a number of additional nutrition

plans that might be appropriate. For example, the Paleo diet has been associated with improved insulin sensitivity and lower levels of inflammation. Many of the benefits of a Paleo diet may be due to the role of insulin (51). By reducing carbohydrate intake, the Paleo diet leads to greater insulin sensitivity and greater insulin sensitivity is associated with reduced food intake and lower rates of obesity. A sample of 24 pigs was randomly assigned to a Paleo diet (vegetables, fruit, meat and limited tubers) or a cereal-based swine diet. At 17 months, the Paleo group weighed 22% less and was more insulin sensitive. CRP levels were 82% lower in the Paleo group and blood pressure was 13% lower. Despite being an animal study, reductions in inflammation are particularly promising given the link between inflammation and schizophrenia.

The Paleo and MedDi diets have been directly compared in a sample of individuals with type-2 diabetes and heart disease (50). After 12 weeks, blood glucose tolerance improved more in the Paleo group. In a follow-up study, the Paleo diet was compared to a recommended diabetes diet (whole grains, low fat dairy, fruit, and vegetables) (52). The study used a cross over design where patients spent time on each diet. Time on the Paleo diet was associated with greater improvements in weight loss, blood pressure, triglycerides, and blood glucose. Thus the Paleo diet was associated with better glucose control than the diet designed to control blood sugar. Removing grains from the diet enabled individuals on the Paleo diet to have lower glucose than individuals on a diabetes diet which remarkably encourages the consumption of a high carbohydrate diet. A systematic review of the research on the Paleo diet has been performed with results strongly indicating the benefits of the diet on metabolic and cardiovascular health markers (53). We focused our discussion on the Mediterranean diet because of the much greater body of research supporting the diet.

Implications for treatment

Along with medication management, patients should receive nutrition counseling as a standard component of treatment. The proposed dietary intervention is based on research that has argued that schizophrenia has an autoimmune component (e.g., 2), and for some people schizophrenia may be an autoimmune condition that is treatable (26). Such counseling should promote the avoidance of grains as well as seed-based oils that are found in almost all processed foods (e.g., cookies, crackers, pre-packaged meals). Instead, patients should be encouraged to consume foods consistent with the MedDi such as lean proteins, vegetables, some fruits, nuts, and seeds, along with healthy fats such as avocados, olive oil and coconut oil. Individuals with schizophrenia have greater insulin resistance, gluten sensitivities, and inflammation than people without schizophrenia. In addition, the side effects of the medication include weight gain, diabetes, high cholesterol, and high blood pressure. It is hypothesized that adherence to a grain-free whole foods diet will improve all of these markers.

The hypothesized effects of a gluten-free grain-free nutritional intervention are provided in Table 1. Based on the limited results of Kalaydjian et al., (34) and Genuis and Lobo (37), it is hypothesized that the nutritional intervention would result in improved symptomatology for some individuals with schizophrenia. In particular, gains should be seen in individuals with significant inflammation and antibodies due to chronic inflammation.

As noted earlier, many patients with schizophrenia were moderately to highly sensitive to gluten (9). Even more individuals may be 'somewhat' sensitive to gluten. Gluten-free diets are well known to improve the health of people with gluten sensitivity. While a relatively small percentage of the general population is gluten sensitive, a much higher percentage of people with schizophrenia may benefit from avoiding gluten. Thus, the nutritional intervention is hypothesized to reduce inflammation and the presence and symptoms associated with autoimmune conditions including insulin resistance. Finally, the nutritional intervention is hypothesized to improve the negative health markers

Table 1: Hypothesized effects of dietary intervention

At the time of onset of symptoms	Side effects of medications	Hypothesized effects of diet	Measures
Psychiatric symptoms		Improved symptoms	
Insulin resistance		Improved glucose control	A1C
		Reduced insulin receptor antibodies	Ir-ab
Inflammation		Reduced inflammation	CRP
Gluten sensitivity		Reduced anti-gliadin antibodies	IgA, IgG, tTG
Anti-NMDA receptor antibodies		Reduced anti-NMDA antibodies	NMDA-ab
	Weight gain	Weight loss	Weight, body measurements
	Diabetes	Improved glucose control	A1C
	Cholesterol	Lower LDL and triglycerides	LDL, triglycerides
		Higher HDL	HDL
	Blood pressure	Lower blood pressure	Blood pressure

Notes: A1C – hemoglobin A1C; Ir-ab – insulin receptor antibodies; CRP – C-reactive protein; IgA – anti-gliadin antibodies; IgG – anti-gliadin antibodies; NMDA-ab – anti-NMDA receptor antibodies; LDL-low density lipids; HDL-high density lipids

associated with antipsychotic treatment (e.g., weight gain, diabetes, high cholesterol, and high blood pressure). The MedDi has been consistently found to improve health outcomes for subjects. A medication that had the potential to improve the health of that many people with schizophrenia would be a blockbuster medication. Public health care systems (e.g., Medicaid) should recognize the role of nutrition as part of a treatment regimen and consider such counseling to be a reimbursable expense.

Another aspect of a nutrition based intervention is the relatively low cost of the intervention. The primary cost of the intervention would be the costs associated with nutritional counseling. In addition, given that most people with schizophrenia have limited financial resources, some type of subsidy might be needed to make nutritious food affordable. However, these costs would be relatively minor compared to the substantial inpatient, outpatient, and pharmaceutical costs incurred by Medicaid programs for people with schizophrenia. Thus, a relatively small effect on emergency room use, inpatient stays, other types of crisis stabilization, and even perhaps medication needs would make such an intervention cost effective.

An intervention should also take into account that people with schizophrenia are very heterogeneous, and often have numerous nutritional deficiencies. Many interventions focus on a single deficiency, for example supplementing with folate or vitamin D, and are not likely to have a substantial impact on patients as a scientific research approach focuses on changing a single variable and doesn't correct remaining deficiencies. Thus, instead of scientifically testing a single nutrient, the goal of an intervention should be to utilize existing knowledge derived from research and develop an intervention tailored to the specific needs of each individual patient. Finally, there is a continued need to link research with practice. In general, there remains a significant gap between academic knowledge and

practice at the state and community level (54). While there exists a considerable research base connecting schizophrenia and nutrition, the treatment of the disease is often devoid of any nutritional counseling or correction of nutrient deficiencies. The development of a low-cost, easy to implement, nutritional intervention made available to institutional and community mental health providers continues to be needed.

Conclusion

Patients with schizophrenia are at increased risk for a wide variety of negative health markers and illnesses. Such markers may be part of the causal mechanism for developing schizophrenia or may simply be associated with the development of the disease. Others health markers have been shown to be side effects of the antipsychotic medications typically prescribed. Regardless of the mechanism, intervention efforts are needed to reduce the impact of these health makers on individuals. A modified Mediterranean diet was recommended as a potential dietary intervention. The diet has been effective at addressing some of the health problems faced by people with schizophrenia.

While diet was the focus of this paper, there are other behaviors that can be encouraged including exercising and (when necessary) quitting smoking. In addition, alcohol consumption and illicit drug consumption, both common among people with schizophrenia should be addressed. But we anticipate that diet is an area where significant gains can be made to improve health outcomes.

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