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Diet and bipolar disorder: a review of its relationship and potential therapeutic mechanisms of action

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Abstract

Objectives: It is well-accepted that diet quality has an important role in the prevention and treatment of several physical diseases. However, its influence on mental health has received far less attention, although there is increasing evidence to support a relationship with depression. In this narrative review, investigations into the relationship between diet and bipolar disorder are examined, and the potential implications in the management and treatment of bipolar disorder are reviewed.

Methods: We provide a narrative review of the relevant information.

Results: Research is limited, although there are preliminary findings to suggest a relationship between diet and bipolar disorder. Findings from cross-sectional research suggest that people with bipolar disorder consume an unhealthier dietary pattern. This has significant treatment implications as bipolar disorder has a high comorbidity with several physical diseases. In addition, diet also influences several biological processes that are dysregulated in bipolar disorder; namely monaminergic activity, immune-inflammatory processes, oxidative stress, mitochondrial activity and neuroprogression.

Conclusions: The role of diet in bipolar disorder requires further attention in research as it presents as a factor that may contribute to the worsening course of this condition, and may potentially enhance current treatment outcomes.

Introduction

The role of diet in physical health is well acknowledged. Dietary quality is associated with the risk of several noncommunicable diseases including type 2 diabetes, cardiovascular disease, obesity, stroke, hypertension and several forms of cancer [1, 2]. Consequently, dietary changes for the prevention and treatment of these conditions are commonly encouraged. However, in mental health the role of diet has received far less attention, and only recently has interest increased in its relationship to depression. It has been confirmed in recent meta-analyses that better diet quality is associated with a reduced probability or risk of depression [3-5]. Rahe et al. [3] concluded from their meta-analysis that the available literature suggested a protective effect of healthy and Mediterranean dietary patterns on depression, whereas a western dietary pattern was associated with an increased odds of depression. In a meta-analysis by Lai et al. [4] it was concluded that a high intake of fruit, vegetables, fish, and whole grains were associated with a reduced depression risk. Another meta-analysis confirmed a relationship between higher adherence to Mediterranean style dietary patterns and reduced risk for depression, as well as stroke and cognitive impairment [5]. Unhealthy dietary intakes are also associated with poor mental health in children and adolescents [6] while even *in utero* nutritional exposures appear to increase the risk for mental health-related behaviours in children [7-9]. In a systematic review of randomised controlled studies there was also evidence that dietary interventions can improve depression outcomes, although due to the paucity of high-quality studies, further research is required and underway [10, 11].

Bipolar disorder is highly disabling with a lifetime prevalence of 1 and 4% [12]. It is associated with marked occupational, personal and social impairment and is accompanied by poor physical health and early mortality. In fact, people with this disorder on average die 10-20 years earlier than the general population, with suicide accounting for approximately 15% of deaths and cardiovascular disease accounting for roughly 35-40% of deaths [13].

Bipolar disorder is a heterogeneous disorder with significant symptom variance within diagnostic subtypes that often varies with illness duration [14]. While the pathophysiology of bipolar disorder remains elusive, studies over the past decade suggest that it is associated with disturbances in several areas. These include alterations in several structural brain regions, neuroendocrine and monoaminergic transmission, immune/ inflammatory processes, mitochondrial activity, oxidative stress, and neuroprogression [15, 16]. Although genetics plays a significant role in the susceptibility to this illness, several psychological, environmental and lifestyle factors also appear important. For example, life stressors and trauma (prenatal through to adulthood) [17, 18], prenatal and early childhood illness [19, 20], drug and alcohol exposure (prenatal through to adulthood) [21], personality factors [22], and even nutritional deficiencies comprising omega-3 polyunsaturated fatty acids (PUFAs) [23], and iron [24] are postulated to be associated with the development and/or exacerbation of this disease.

Investigation into the role of diet in the etiology of bipolar disorder has received surprisingly scant attention. The purpose of this article is to provide a narrative review of research conducted on diet and bipolar disorder, address the potential impact of diet on bipolar disorder and its several medical comorbidities, and discuss the potential of dietary interventions for bipolar disorder.

A review of relationship between diet and bipolar disorder

The PubMed, Google Scholar, and PsycInfo databases were searched from all years of record until February 2015, using the terms "diet", "nutrition" and "bipolar disorder". The reference lists of relevant papers were also examined to locate additional studies that were not identified by the database searches. Five studies were identified and are summarised in Table 1. All studies comprised cross-sectional designs and used varying measures to assess diet quality and bipolar severity, thereby making cross-study comparisons difficult.

Elmslie et al. [25] used a 24-hour diet recall and 4-day estimated diet record to compare dietary patterns of people with bipolar disorder (n=89) to an age- and sex-matched comparison group (n=445). They found that people with bipolar disorder consumed more total carbohydrate, sucrose, non-alcoholic beverages, sweetened drinks, cakes, and sweets. Women, but not men, also had a greater total energy intake. It is important to note that 87% of the bipolar group were on psychotropic medications thereby presenting a likely important confounding factor influencing dietary intake.

From cross-national comparisons, Noaghiul & Hibblen [26] demonstrated that greater rates of seafood consumption were associated with lower lifetime prevalence rates of bipolar I disorder, bipolar II disorder, and bipolar spectrum disorder. These findings are tempered by the lack of control for confounding variables or variability in the definition and diagnosis of bipolar disorder across countries.

Based on the Veterans Affairs national psychosis registry, which includes a register of people diagnosed with bipolar disorder, Kilbourne et al., [27] found that people with bipolar disorder (n=1945) were more likely than those with no serious mental disorder (n=3086) to report eating only one meal a day, eating alone, and having difficulty obtaining or cooking food. However, there was no difference in reported fruit and vegetable intake, which may reflect the generally low level of intake in the general population [28]. Several demographic and clinical factors were controlled for in this study including gender, age, race/ethnicity, marital status, current employment, smoking, financial strain, substance use disorder and antipsychotic use [27].

A cross-sectional analysis comparing 23 women with bipolar disorder to women with no past or current depressive or anxiety disorders was undertaken by Jacka and colleagues [29]. Their findings demonstrated that people with bipolar disorder consumed a higher energy/ kilojoule intake and a diet with a higher glycaemic load. After statistical adjustment for energy intake, respondents with bipolar disorder also had lower scores on a 'traditional' dietary pattern (i.e., vegetables, fruit, beef,

lamb, fish and wholegrain foods). They also reported higher scores on a 'western' dietary pattern (i.e., meat pies, processed meats, pizza, chips, hamburgers, white bread, sugar, flavoured milk drinks and beer) although this relationship became non-significant after adjustment for energy intake. Interestingly, bipolar patients also reported a higher intake of modern foods (fruits and salads, plus fish, tofu, beans, nuts, yoghurt and red wine). The authors postulated that this may reflect attempts by people with bipolar disorder to improve symptoms through healthy dietary changes. This behaviour has been confirmed by a recent study where previously depressed individuals who had sought professional treatment reported consuming a healthier diet, suggesting that some may attempt to improve their depressive symptoms through dietary modification [30].

Finally, Noguchi et al, [31] found that in people with bipolar disorder attending a psychiatric clinic (n=75), physical and psychiatric symptoms were more pronounced in those reporting an infrequent intake of vegetables, soy products, seaweed, and fish products. This correlation remained significant after adjustment for age, body mass index (BMI) and sex. However, they found that physical, psychiatric and anxiety severity were not associated with fish pattern consumption or a western/meat dietary pattern.

Findings from this initial research suggest a relationship between diet and bipolar disorder, wherein people with bipolar disorder consume an unhealthier diet, and diet quality may influence symptom severity. Unfortunately, studies are scant, comprise only cross-sectional analyses, and most do not adequately control for potential confounding variables. These include medication use, BMI, socio-economic status (SES), comorbid diseases and other drug use. At this time it is therefore unknown whether diet quality has a causative role in bipolar disorder or is simply a lifestyle-based factor associated with this disease. It is possible that sweet and fatty foods are consumed as a food of self-medication; sugar reduces stress-induced cortisol [32] as well as being somewhat addictive [33]. Highly powered, prospective studies controlling for confounding variables are required to help elucidate the role of diet in bipolar disorder. The use of validated dietary measures on clinically-

diagnosed bipolar patients using validated diagnostic instruments are also important to help increase the robustness of findings. Analyses examining the most important dietary components (i.e., macro- and micro-nutrients), dietary patterns (i.e., western, traditional, Mediterranean), and eating habits (i.e., meal frequency, meal skipping) are also important.

What is the potential significance of diet in bipolar disorder?

Dietary modification to combat medical comorbidity

There is a greater comorbidity of bipolar disorder with several noncommunicable diseases. These include type 2 diabetes, metabolic syndrome, cardiovascular disease and obesity [34-36]. These diseases are significantly influenced by lifestyle factors, diet quality being of particular importance. Diet quality therefore has relevance in bipolar disorder by contributing to the increased prevalence of these conditions. This increased disease burden is associated with greater medical costs, polypharmacy use, increased hospitalisations, reduced quality of life and increased risk of early mortality [35]. Given the common problem of weight gain associated with psychotropic interventions, diet also has a role in preventing or minimising this adverse effect. This is especially important as weight gain is a common reason cited for medication non-compliance [37].

There is also evidence to suggest that medical comorbidity in bipolar disorder is associated with greater treatment resistance and illness severity. For example, patients with bipolar disorder and type 2 diabetes or insulin resistance had three times higher odds of a chronic course of bipolar disorder compared with euglycaemic patients [38]. A history of weight cycling was also associated with a greater frequency of manic and depressive episodes [39]. Medical comorbidity is also concerning as bipolar patients have markedly higher rates of mortality after myocardial infarction [40] and there is inferior global cognitive ability in bipolar patients with obesity and treated hypertension [41]. Obesity in bipolar disorder is also associated with greater suicidality [42].

Dietary modification to normalise dysregulated biological pathways

Bipolar disorder is confirmed to be associated with several biological dysregulations. These include disturbances in monaminergic activity, immune-inflammatory processes, oxidative stress, mitochondrial activity and neuroprogression [15, 16]. As outlined by a selection of studies below, all these biological pathways can be influenced by diet composition and quality.

Monaminergic activity: In animal studies the intake of a combination of dietary fat and sugar reduced D_2 receptor signalling [43], and the consumption of a low-protein-high-carbohydrate diet decreased D_2 receptor density [44]. Fasting and high sucrose diets also influenced catechol-O-methyltransferase activity [45, 46]. Dietary fat intake and a ketogenic diet (very low-carbohydrate, high-fat diet) influenced the expression of glutamic acid decarboxylase and brain GABA concentrations [47, 48]. Finally, in a human study, hypercaloric high-fat-high-sugar snacking decreased serotonin transporters in the human hypothalamic region [49]. Interestingly, in an animal study using an unpredicted chronic mild stress (UCMS) model, a high-fat diet regimen prevented the antidepressant fluoxetine from abolishing UCMS-induced behavioural changes [50].

Immune-inflammatory processes: A Mediterranean diet and a greater consumption of fruit and vegetables has regularly been associated with reduced inflammation [51-53]. In contrast, consuming a western dietary pattern is commonly associated with increased inflammation as demonstrated by elevated C-reactive protein and interleukin-6 [54, 55].

Oxidative stress: Markers of oxidative stress such as malondialdehyde (lipid peroxidation) and 8-hydroxy-2'-deoxyguanosine (DNA oxidation) were lowered after the consumption of a Mediterranean diet or increased fish intake [56, 57]. Calorie restriction also positively influenced the oxidant/antioxidant balance, particularly via its effects on glutathione concentration [58, 59].

Neuroprogression: In a human study, consuming a Mediterranean diet was associated with increased levels of brain-derived neurotrophic factor (BDNF), a neurotrophin that supports the

survival, growth and differentiation of neurons [60]. There are also extensive data from preclinical studies implicating diet in hippocampal neurogenesis [61]. In an animal study, caloric restriction increased BDNF concentrations [62], whereas a high-fat diet lowered BDNF expression [63, 64]. Consuming a high-fat diet also decreased the quantity of newly generated cells in the dentate gyrus of the hippocampus [63]. Zainuddin and Thuret [61] have reviewed findings demonstrating adult hippocampal neurogenesis is influenced by caloric intake, meal frequency, food texture and meal composition (e.g., sugar, fat, omega-3 PUFAs, zinc, and polyphenols such as curcumin and resveratrol).

Mitochondrial activity: Compared with rats on a calorie-restricted diet, mitochondrial efficiency and oxidative damage in skeletal muscle were significantly increased, while antioxidant defence was significantly lowered in food-restricted rats fed a high-fat diet [65]. A ketogenic diet up-regulated mitochondrial antioxidant status, and protected mitochondrial DNA from oxidant-induced damage [66].

Despite evidence through animal, and a selection of human studies, that diet can influence the above-mentioned biological processes, its effects in patients with bipolar disorder are currently unknown. Whether dietary changes can normalise such dysregulations in a clinical sample requires investigation. Furthermore, its relevance to symptomatic change also needs to be investigated as it is currently unknown whether normalisation in these pathways are necessary for clinical improvement. To our knowledge there is only one study, currently underway, investigating dietary improvement as a treatment strategy for mood disorders [11]. This study may throw light on this question.

Conclusion and directions for future research

Investigations into the role of diet in bipolar disorder are still in their infancy. Although the impact of diet on physical health is well acknowledged, its role in mental disorders have received

far less attention. As demonstrated from this review, diet has potentially significant implications for the treatment of bipolar disorder. At the very least, it has a role in the management and prevention of several highly comorbid physical diseases including type 2 diabetes, metabolic syndrome, obesity and cardiovascular disease. Moreover, it theoretically has a role in the prevention and treatment of bipolar disorder, although further research is required. Because diet can influence several biological pathways that are regularly dysregulated in bipolar disorder it presents as a natural intervention that can help normalise these disturbances. However, as discussed above, it remains to be determined whether normalisation in these pathways are necessary for symptomatic improvement in bipolar disorder.

Highly powered, prospective studies adequately controlling for important confounding variables such as BMI, SES, medication use and medical comorbidity are necessary to enhance our understanding of the role of diet in bipolar disorder. Currently, studies have only comprised cross-sectional designs thereby preventing conclusions about the causative influence of diet on the development and exacerbation of bipolar symptoms. In addition, an examination of dietary interventions on bipolar disorder are also needed. As an adjunct to pharmacological and psychological interventions it has the potential to enhance treatment efficacy.

Although research on single nutrient therapies has not been covered in this review, its influence on disturbed biological pathways in bipolar disorder and the enhancement of treatment efficacy in conjunction with whole-of-diet interventions also merits consideration. Promising findings have been demonstrated for the use of omega-3 PUFAs, n-acetyl cysteine, magnesium and folic acid in bipolar disorder [67, 68]. There have also been positive results for a proprietary multi-nutrient formula in several open-label studies [69]. However, most studies are poorly designed and contain small sample sizes. Deficiencies in such nutrients and in insufficiency resulting from genetic polymorphisms can influence several of the previously-mentioned biological pathways [70, 71] and requires further investigation.

Ongoing research into the relationship between diet and bipolar disorder is urgently needed. To date, no study has yet been conducted examining the potential of whole-of-diet interventions for this disorder. This is concerning as diet has proven an important component for the enhancement of physical health but its role in mental health, along with other lifestyle factors such as exercise, require greater attention in research.

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Contributors

Adrian Lopresti conducted a literature search and wrote the first draft of this manuscript. Felice Jacka reviewed the manuscript and provided feedback, corrections and recommendations on further drafts of this manuscript. All authors contributed to and have approved the final manuscript.

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Conflict of interest

The author reports no biomedical financial interests or potential conflicts of interest.

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