

# Nutrition and Bipolar Depression

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## KEYWORDS

- Bipolar depression • Diet • Nutrition • Omega-3 fatty acids • *N*-acetylcysteine
- Vitamin D • Mediterranean diet

## KEY POINTS

- Increasing research has identified the quality of one's diet as a potential major contributor to mood stability and expression. Mediterranean dietary patterns compared with Western dietary patterns may be supportive of good mental health in general and bipolar disorder specifically.
- Patients with bipolar disorder tend to have a poorer quality diet, with increased sugar, high fat, and carbohydrate intake. This may contribute to both poor physical health and mental health.
- Omega-3 fatty acids and *N*-acetylcysteine have been demonstrated to be helpful dietary supplements in the control of bipolar depressive symptoms.

## INTRODUCTION

Nutritional psychiatry is an emerging discipline focused on the relationship between dietary patterns and mental health disorders.<sup>1</sup> Whereas the role of diet in physical health is well-acknowledged, the relationship between diet and mental health has received much less attention. The quality of diet is well known to be associated with many diseases, such as cardiovascular disease, type 2 diabetes, hypertension, and stroke. Therefore, changes that promote good dietary habits are commonly encouraged by health care providers to both prevent and treat these illnesses. However, the role of diet in mental health is much less known and with limited promotion among clinicians. Nevertheless, the impact that nutrition may have on the brain is self-evident. The brain operates at a very high metabolic rate, commanding much of the body's nutrient intake in order to support its structure as well as power its function. Nutritional psychiatry postulates that diet may contribute to either resilience or risk in mental illness.

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Over the last decade, there have been an increasing number of well-designed studies that have demonstrated the association of a healthy diet with improvements in a variety of mental illnesses and symptoms, such as depression, anxiety, attention, and irritability.<sup>2-9</sup> Furthermore, their positive effect sizes suggest certain dietary interventions may be clinically relevant to patients, although as of yet, there are no available data regarding the therapeutic impact of dietary changes on existing mental illness.<sup>10</sup>

The effect of diet in major depressive disorders has recently been an area of more intense study. Two meta-analyses of diet and depression have supported the observation that a Mediterranean-style diet is associated with a protective effect on depression (as well as stroke and cognitive impairments), whereas a Western dietary pattern is associated with an increased likelihood for depression.<sup>4,11</sup> In another meta-analysis, Lai and colleagues<sup>3</sup> concluded that diets that emphasized fruit, vegetables, fish, and whole grains were associated with a reduced depression risk. These results suggest that what we eat may make a difference in how we think, or at least in how we feel.

Evaluation of the role nutrition and nutraceuticals may have in bipolar disorder has received only very limited research attention. At the turn of the century, the data that were available were often cobbled from secondary and experimental analyses of studies with other foci of attention, often confounding clear interpretation.<sup>12</sup> However, with the recent findings of the role that diet may play in depression and a new framework for understanding the relationship between nutrition and affective symptoms, there has been an increased focus on nutrition in bipolar disorder.

The purpose of this article is to review the recent research conducted on nutrition and bipolar disorder, with special emphasis on its depressive phase. Also discussed is the potential of nutritional interventions for bipolar depressions.

## NUTRITION IN BIPOLAR DISORDER

In the past century, the food industry has undergone an enormous transformation, resulting in substantial increases of production, availability, advertising, and sale of food.<sup>12</sup> These changes have caused profound shifts in the composition of diets globally, which in turn, has contributed to the increased burden of diseases (such as cardiovascular disease, stroke, and hypertension) during the latter part of the 20th century.<sup>13,14</sup> As noted above, the Western diet has come under increased scrutiny for its role in these illnesses. A Western diet reflects a higher consumption of foods such as processed meats, pizza, chips, hamburgers, white bread, sugar, flavored drinks, and beer, a pattern that reflects high intakes of saturated fat, sodium, nitrites, and refined carbohydrates, including sugars. In health research, this dietary pattern is frequently compared with a Mediterranean diet, which emphasizes consumption of fruits, vegetables, fish, and whole grains, while limiting unhealthy fats.

Recent data from the SUN (Seguimiento Universidad de Navarra) Cohort study in Spain, an ongoing longitudinal study of 10,094 adults, demonstrated an inverse association between the level of adherence to a Mediterranean dietary pattern and the risk for depression.<sup>7</sup> Similarly, data from the Whitehall II cohort, a British based longitudinal study with 3486 participants, found an increased risk of self-reported depression after 5 years for those adhering more strongly to a Western-style diet pattern, and a reduced risk for those following a whole-foods diet pattern.<sup>15</sup> These findings have raised the question about diet and bipolar disorder as well, especially given the concern that many bipolar patients are at a higher risk of metabolic syndrome.

What kind of diets do patients with bipolar disorder typically have? There have been a few cross-sectional studies that have assessed the diets in small groups of bipolar patients. Jacka and colleagues<sup>16</sup> compared the diets of 23 women with bipolar

disorder with 691 women without any history of depression. They found that bipolar patients had a diet with both higher energy intake and higher glycemic load than controls. Furthermore, the diet scores showed more consumption of the Western-style dietary pattern and lower scores for a traditional dietary pattern (vegetables, fruit, beef, lamb, fish, and whole-grain foods). Elmslie and colleagues<sup>17</sup> reviewed the previous 24-hour food consumption of 89 bipolar outpatients compared with 445 age- and sex-matched control subjects. They found that bipolar patients consumed more total carbohydrates, sucrose, nonalcoholic beverages, sweetened drinks, cakes, and sweets. Kilbourne and colleagues,<sup>18</sup> in their review of nutrition in veterans, evaluated lifestyle reports of 1945 veterans with bipolar disorder and compared that with 3086 veterans without diagnosed mental disorders. They did not find a difference in reported fruit and vegetable intake, but observed that this actually reflected the generally low level of intake in the general population.

What these studies underscore is that bipolar patients tend to consume an unhealthy diet, but it is unknown how diet and bipolar disorder may interact with each other. It is possible that poor diet quality may have a causative role in bipolar disorder. It is possible that poor diet quality represents a lifestyle factor associated with the illness. It is possible that poor diet quality may be caused by the treatments for the disease. It is possible that sweet and fatty foods are preferentially consumed by bipolar patients as a method of self-medication.<sup>19</sup> It is also possible that diet quality and bipolar disorder interact in more than one of these ways.

For example, in the analysis by Kilbourne and colleagues<sup>18</sup> of nutrition in veterans, behavioral factors in patients with bipolar disorder were also identified that would contribute to an unhealthy diet in anyone engaging in these behaviors. They noted that the bipolar group was much more likely to report eating only one meal a day, eating alone, or having difficulty in obtaining/cooking food. Poor nutrition access or limited diet options for bipolar patients may directly contribute to poor diet quality. The disease may be the cause of unhealthy lifestyle decisions.

Furthermore, in the diet review by Elmslie and colleagues,<sup>17</sup> the investigators hypothesized that the cause of the bipolar group's poor dietary patterns (increased consumption of sweets in the bipolar group) may be a medication-induced phenomena, because 87% of the sample were on psychotropic medications, which may significantly cause weight gain and metabolic syndrome. In other words, the treatment of the disease may be the cause of unhealthy diet patterns.

Lopresti and Jacka<sup>19</sup> noted that sugar may reduce stress-induced cortisol and therefore may be used excessively by bipolar patients, who tend to have more life stressors (or poorer coping skills). Furthermore, one of the primary symptoms of bipolar depression/mania is a change in appetite and weight, suggesting that the disease may induce the choice of unhealthy diet patterns.

Finally, others have suggested that diet may actually cause or worsen bipolar disease. Whereas in the past, this hypothesis was thought to be somewhat far-fetched, new understandings of bipolar disorder have caused us to rethink this possibility. Because of the nebulous association between diet and bipolar disease, further studies are required that control for the confounding variables in order that the role of diet in bipolar disorder may be better assessed.

## **THEORETIC FRAMEWORK FOR INTERACTION BETWEEN NUTRITION AND BIPOLAR DISORDER**

Despite the increasing evidence of the role of diet in bipolar disorder, acceptance and translation to practice have often been minimized because of the lack of clear

theoretic frameworks on which researchers can construct informed hypotheses and clinicians can integrate into effective interventions.<sup>20</sup> However, the increasing research on biological pathways that are dysregulated in patients with bipolar disorder has provided new insights into how nutrition may contribute to illness development. The improved understanding of inflammatory processes, immune functioning, and neuroprogression in bipolar patients has provided new hypotheses that challenge the understanding of mood disorder development and treatment. Lopresti and Jacka<sup>19</sup> conducted a review of several of these biological pathways that have shown dysregulation in bipolar disorder, and how diet may interact to induce or sustain these dysregulations. They include monoaminergic activity, inflammatory processes, oxidative stress, mitochondrial activity, and neuroprogression.

### ***Monoaminergic Activity***

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For the past 50 years, the focus of mood disorder treatment, especially depressive episodes, has been on the monoaminergic neurotransmitters dopamine, serotonin, and norepinephrine. It is thought that alterations in neurotransmitter regulation and availability may cause a cascading effect on mood dysregulation. Animal studies have determined that high-fat diets may directly affect dopaminergic, noradrenergic, and serotonergic activity throughout the brain.<sup>21–23</sup> Furthermore, dysregulated dopaminergic signaling observed in obese rats that were fed a high-fat diet appeared to induce further craving for fatty foods.<sup>24</sup> Ketogenic diets that have been reported to help with depressive symptoms and bipolar II disorders<sup>25</sup> may exert their effect by increasing dopaminergic activity in the mesolimbic system.<sup>26</sup> Animal studies have also found that a high-fat diet decreased serotonin levels in the body<sup>27</sup> and prevented fluoxetine from effectively treating stress behaviors.<sup>28</sup> In humans, hypercaloric high-fat/high-sugar snacking has been noted to decrease serotonin transporters in the hypothalamus.<sup>29</sup> These findings suggest that unhealthy diets may not adequately support the neurotransmitters involved in mood regulation, or may even worsen mood symptoms.

### ***Inflammatory Processes***

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Drs Rosenblat and McIntyre<sup>30</sup> have reviewed the potential role of inflammation in bipolar disorder in a separate article in this issue. This systemic inflammation may be caused by several identified processes, but 2 of these are nutritionally related: diet and vitamin D deficiency.<sup>31</sup> There has been consistent evidence that a Mediterranean diet and greater consumption of fruit/vegetables have been associated with reduced inflammation,<sup>32–35</sup> while a Western diet pattern has been associated with increased inflammation.<sup>36</sup> These relationships are further explored in the later discussion of omega-3 fatty acids.

### ***Neuroplasticity and Neuroprogression***

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In the last decade, there has been a robust research interest in brain plasticity in mood disorders. Brain-derived neurotrophic factor (BDNF) is a neuropeptide that supports the growth and differentiation of neurons. Studies have shown that a Mediterranean diet was associated with increased levels of BDNF,<sup>37</sup> suggesting increased ability to nurture neurons. Numakawa and colleagues<sup>38</sup> have reviewed the interactions between diet and altered BDNF activity (noting also its association with inflammation). Animal studies have suggested that high-fat diets lower BDNF expression and decrease the quantity of newly generated cells in the hippocampus.<sup>39,40</sup> In their review of nutrition and neurogenesis, Zainuddin and Thuret<sup>41</sup> have found that caloric intake, meal frequency, and a diet composition of fats and sugars directly affected

hippocampal development. More recently, Jacka and colleagues<sup>42</sup> found that subjects who maintained a Western dietary pattern over a 4-year period had a progression toward smaller left hippocampal volume than others on more healthy diets.

### ***Oxidative Stress***

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A growing body of evidence has implicated oxidative stress and mitochondrial dysfunction in bipolar disorder. Mitochondria are responsible for energy generation and are extremely active in the brain, which is an oxygen-rich and highly energy-dependent organ. Impaired energy metabolism triggers pro-apoptotic signaling and oxidative damage; this in turn impedes mitochondrial DNA repair. These processes can potentiate each other, leading to a vicious cycle, whereby mitochondrial dysfunction leads to oxidative stress, which then leads to further mitochondrial damage and dysfunction. Studies have shown that diet may significantly affect mitochondrial functioning. A ketogenic diet enhances cellular metabolic and mitochondrial function, upregulates mitochondrial antioxidant status, and protects mitochondrial DNA from oxidant-induced damage.<sup>43–45</sup> In addition, a Mediterranean-style diet and elevated fish consumption have been associated with decreased markers for oxidative stress.<sup>46–48</sup>

## **BIPOLAR DEPRESSION AND NUTRITIONAL SUPPLEMENTS**

The above examples of nutritional interactions with dysregulated biological pathways have provided better scientific hypotheses for understanding the potential diet/mood interactions. In their review of diet and depression, O'Neil and colleagues<sup>10</sup> noted that studies have consistently identified unhealthy dietary patterns as being associated with depression. They suggested that what is excluded from the diet may be as important as what is included. Although food is not the same as medication, it is increasingly evident that what one eats affects biological processes that in turn may affect mood. As of yet, the exact mechanisms in patients with bipolar disorder are not known, so consistent guidelines for dietary adjustments have not been codified. However, there are several specific examples that have been shown to be helpful in clinical practice.

### ***Omega-3 Fatty Acids***

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One frequently mentioned dietary modification for use in bipolar disorder is the addition of omega-3 fatty acids. These polyunsaturated fats (PUFAs) have numerous health benefits, are significantly underrepresented in Western diets, and are thought to play a key role in promoting brain health. Omega-3 PUFA docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), which are derived from marine sources (including fish and algae), are typically considered crucial for brain health and mental disorders.

The brain is primarily composed of lipids in a ratio of saturated fatty acids, monounsaturated fatty acids, and PUFAs. The principal PUFAs in the brain are the omega-6 fatty acid arachidonic acid (AA; 20:4*n*-6) and the omega-3 fatty acid DHA (22:6*n*-3). AA and DHA are acetylated into the *sn*-2 position of membrane phospholipids of neurons. The enzyme phospholipase A<sub>2</sub> "activates" these 2 PUFAs by hydrolyzing the acyl ester bond. DHA and AA then exert opposing effects on the protein kinase C (PKC) signaling transduction pathway and the multiple downstream synaptic events regulated by PKC.<sup>49</sup> Eicosanoids (signaling molecules made by oxidation of 20-carbon fatty acids) derived from AA are pro-inflammatory, whereas docosanoids (signaling molecules made by oxygenation of 22-carbon essential fatty acids) derived from DHA are anti-inflammatory. Thus, if the membrane AA:DHA ratio is increased, there would be an increased inflammatory response detrimental to normal brain function.<sup>50</sup>

Emerging evidence has indicated that an inadequate intake of omega-3 PUFA may be associated with bipolar disorder. First, Noaghiul and Hibbeln<sup>51</sup> have noted in a multinational study that diets richer in the intake of fatty fish (foods high in omega-3 fatty acids) were associated with a lower lifetime prevalence rate of bipolar I, bipolar II, and bipolar spectrum disorders. Second, Evans and colleagues<sup>52</sup> found there was a reduced intake of omega-3 and omega-6 PUFA in the diets of patients with bipolar disorders. Third, Bly and colleagues<sup>53</sup> demonstrated that the diet of bipolar patients has a higher ratio of omega-6 to omega-3 PUFA (reflecting a Western dietary pattern). Fourth, animal studies have demonstrated that diets deficient in omega-3 PUFA alter monoamine systems in limbic structures.<sup>54</sup> Fifth, evidence from peripheral tissue fatty acid composition studies suggests that patients with bipolar disorder exhibit omega-3 PUFA insufficiency relative to normal controls.<sup>55,56</sup> Sixth, in brain autopsy studies of patients with bipolar disorder, DHA was significantly lower in the orbital frontal cortex (OFC) of bipolar patients relative to age-matched normal controls, and DHA composition was inversely correlated with elevations in AA and stearic acid conversion/metabolism.<sup>50</sup> (Of note, bipolar patients that committed suicide also exhibited selective deficits in OFC DHA composition, a finding that is consistent with studies in unipolar depression.) Seventh, mood stabilizers have been shown to specifically inhibit membrane turnover and downstream signaling of AA, but not DHA, suggesting that mood stabilizer activity may act in part by improving the ratio of AA:DHA activity.<sup>57</sup> Finally, systematic reviews of clinical trials using omega-3 fatty acids have consistently demonstrated a significant effect of omega-3 PUFA in ameliorating the depressive (but not manic) symptoms in bipolar disorder.<sup>58-60</sup>

As noted above, **there are 2 principal types of omega-3 PUFA: DHA and EPA.** Several reviews<sup>61,62</sup> have suggested that EPA, rather than DHA, is responsible for the beneficial effects of omega-3 PUFA in depressive disorders, and that **supplements containing EPA greater than 60% were most effective against primary depression.**<sup>58</sup> This finding is somewhat surprising given that DHA is a major structural component of neuronal membranes and EPA is present at relatively much lower levels. There are several possible explanations for this finding, including the fact that DHA is poorly incorporated into human brains and EPA may facilitate this. Other explanations include the anti-inflammatory effect of EPA-derived eicosanoids, its efficacy at reducing the inflammatory cytokines, tumor necrosis factor- $\alpha$ , interleukin (IL)-6, and IL-1b, and increasing *N*-acetyl-aspartate in the brain (suggesting a neuroprotective role).<sup>58</sup> However, methodological issues may also have biased the results in favor of EPA-containing prescriptions. The dose of EPA varied in each study, so the recommended dose in depressive disorders may be anywhere from 1.0 g to 10 g per day.<sup>63</sup>

The evidence for use of omega-3 PUFA in bipolar disorder suggests a positive effect in depression but not mania; however, the limited data available should give the clinician caution in their clinical expectations. Furthermore, current evidence only supports its use as an adjunctive treatment, not an alternative to standard psychopharmacologic interventions. On the positive side, omega-3 PUFAs do not appear to have any significant adverse effects and may be helpful for general health.<sup>59</sup>

### ***N*-acetylcysteine**

As noted above, recent evidence has implicated the relevance of systemic inflammation and oxidative damage in bipolar disorder.<sup>64</sup> This evidence is supported by 5 prominent findings: (1) evidence of dysregulated oxidative defense in bipolar disorder, (2) effects of oxidative stress on cellular constituents (particularly lipids and mitochondrial DNA), (3) concordant structural evidence of neuroprogressive processes, (4) studies that have noted that bipolar treatments have significant influences

on the oxidative processes, and (5) association studies of polymorphisms of key genes in the glutathione pathway.<sup>65</sup> Researchers therefore are interested in treatments that may target these pathways.

Glutathione is the principal endogenous antioxidant in the brain. It neutralizes reactive oxygen and nitrogen species and is responsible for maintaining the oxidative balance in the cell. Glutathione is vulnerable to depletion and substantially reduced in patients with bipolar disorder.<sup>66</sup> However, oral administration of glutathione is not adequate to replenish insufficiencies because it is rapidly hydrolyzed by first-pass mechanisms, and then only poorly crosses the blood-brain barrier. Therefore, researchers have focused on the use of *N*-acetylcysteine (NAC). NAC is a precursor to glutathione and provides L-cysteine, the rate-limiting factor in the glutathione synthesis pathway.<sup>67</sup> In addition, NAC has been shown to have anti-inflammatory properties that are linked to oxidative pathways.<sup>66</sup> **Clinical trials in bipolar disorder have found NAC to significantly improve depressive symptoms and functional outcomes for patients during the maintenance phase of treatment over a 24-week period.**<sup>65,68,69</sup> Secondary analyses also noted that NAC was helpful for bipolar patients with full depressive episodes and bipolar II patients.<sup>70,71</sup> The dose of NAC was either 500 mg or 1000 mg twice a day. Although these data support its use in improving depressive symptoms in maintenance treatment, trials are currently underway to assess its use as adjunctive therapy for acute bipolar depressive episodes.<sup>72</sup> The tolerability profile of NAC appears benign, but it should be noted that data on its safety and tolerability in long-term use are limited.

### **Vitamins**

Vitamin D and folate are essential for good neuronal functioning and have been shown to be helpful in depression. Low levels of vitamin D have been associated with bipolar disorder; however, there have not been any studies looking at the efficacy of vitamin D treatment in bipolar disorder.

**Folic acid and folate (converted into L-methylfolate in the body) have been increasingly used in depressive disorders.** It is thought that folate may affect depression treatment by facilitating neurotransmitter production (modulating homocysteine and S-adenosyl methionine) and improving DNA repair and methylation.<sup>73,74</sup> However, evidence for its use in bipolar disorder is limited. Only one published study assessed the use of folic acid augmentation (200 µg) versus placebo in a small sample of bipolar depressed patients treated with lithium.<sup>75</sup> No significant difference was observed between the 2 groups in their depressive symptoms after 52 weeks. The negative finding of the folic acid study may be due to vitamin form, because folic acid, unlike naturally occurring folate, must first be reduced before it can cross the blood-brain barrier. **Beneficial associations in depression studies have more often been found with natural folate and L-methylfolate rather than folic acid.**<sup>76</sup>

Inositol, a vitaminlike substance found in many plants and animals, is a glucose isomer precursor of phosphatidyl inositol, an important second messenger system that is linked to neurotransmitter receptors.<sup>77</sup> Chengappa and colleagues<sup>78</sup> conducted a 6-week controlled trial using 12 g of inositol in 24 bipolar patients with depression. They found a significant reduction in depressive symptoms after 3 weeks, but this improvement was not maintained for the full 6 weeks. Another study of 5 to 20 g of inositol augmentation to mood stabilizers in 17 bipolar patients also found no significant improvement in mood outcomes.<sup>79</sup> However, possible efficacy was suggested by results from one of the STEP-BD substudies, a 16-week open-label augmentation of mood stabilizers with 1 of 3 compounds: lamotrigine, inositol, or risperidone, conducted in 66 treatment-resistant bipolar depressed subjects. All patients had

demonstrated poor response to 12 weeks of a standard treatment or one of the randomized care pathways, or had a history of failure to respond to at least 2 antidepressants or an antidepressant plus mood stabilizer. The investigators found the rate of recovery was 23.8% with lamotrigine, 17.4% with inositol, and 4.6% with risperidone.<sup>80</sup> There is only limited information on the safety profile of inositol, so clinicians should use caution when considering its use.

## SUMMARY

As with physical conditions, bipolar disorder is likely to be significantly impacted by diet and nutrition. Dietary patterns have been associated with bipolar disorder, including the potential protective effect of a Mediterranean diet. In addition, there is evidence in bipolar disorder of system inflammation and altered omega-3 fatty acid metabolism, both conditions that can be improved with dietary intervention.

Unfortunately, the evidence base examining the relationship between diet and bipolar disorder at this time is relatively thin. However, based on evidence for other brain disorders, including unipolar depression, there is optimism that nutritional alterations may have a definite role in the treatment of bipolar disorder as augmenters to pharmacotherapy. **The most promising, in terms of both potential efficacy and safety profiles, are omega-3 PUFA, NAC, inositol, and L-methylfolate.** These nutritional supplements have already been incorporated into some of the published bipolar depression treatment algorithms. The **Canadian Network for Mood and Anxiety Treatment and the International Society for Bipolar Disorders bipolar depression guidelines<sup>81</sup> list augmentation with EPA and NAC among their novel or experimental treatment options,** whereas the **Texas Medication Algorithm Project for bipolar depression<sup>82</sup> lists inositol augmentation as a potential fifth step.** Rakofsky and Dunlop<sup>83</sup> comment that given the limited evidence for these nutritional supplements, their placement at the end of these algorithms is appropriate.

However, more consideration should be given to the larger role of diet and nutrition in bipolar patients at the outset of treatment. Despite clear evidence of a link between nutrition and bipolar disorder, there remains a compelling reason to counsel bipolar patients to improve their diets. Individuals with bipolar disorder are at elevated risk of poor medical outcomes, including cardiovascular disease, diabetes, and metabolic syndrome, all conditions that may be prevented and ameliorated with dietary modification. Increasing intake of fruits, vegetables, nuts, and whole grains, while reducing consumption of saturated fat, processed meats, refined grains, and sugars, will improve a bipolar patient's overall health risk profile and has the potential to improve their psychiatric outcomes as well.

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