

## Diet, Nutrition and Opioid Addiction

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### ABSTRACT

Adequate nutrition and balanced diet are essential for optimum physical and psychological health. This is especially important in individuals with opioid use disorder (OUDs) who typically show mild to moderate micronutrient deficiencies, including iron and B-complex vitamins. Such deficiencies can alter synaptic plasticity, particularly of the mesolimbic dopamine (ML-DA) pathways responsible for control of feeding and processing of emotions, rewards, and cognition, in these individuals. Addiction to food strongly resembles addiction to drugs of abuse. OUDs tend to prefer high salt, fat, and sugar diets, which activate the ML-DA causing euphorogenic effects. Concurrently, the malnutrition OUDs experience encourages cravings and contribute to their drug seeking. To remedy nutritional deficiencies and brain abnormalities in OUDs, we propose that multiple strategies be incorporated into their treatment regimens that will aid individuals to overcome opioid use disorder and decrease risk for relapse in those who have already recovered.

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Adequate nutrition and balanced diet are essential for optimum physical and psychological health. This is especially important to support the recovery of individuals with opioid use disorder (OUDs). Existing evidence have shown that OUDs experience mild to moderate micronutrient malnutrition obscured by the transient compensatory increase in body weight due to high fat and carbohydrate intake [1,2]. The most common micronutrient deficiencies in OUDs include iron and B-complex vitamins such as thiamine, riboflavin, pyridoxine, and folate [3]. Many individuals with OUD also suffer from constipation, diarrhea, and malabsorption problems that impair the metabolism of micronutrients [4,5]. In addition, socioeconomic factors such as food affordability and availability of cooking facilities may also contribute in the prevalence of malnutrition among individuals with OUD [4,6].

The brain plays a major role in appetite and food regulation. The hypothalamus serves as the integrating center of neuronal pathways that inhibits or stimulates food intake. These pathways are controlled by a complex interplay of neurotransmitters on the synaptic receptors. When food is ingested, certain hormones in the gut such as leptin, ghrelin, glucagon-like peptide-1 (GLP1), and insulin are released in the circulation. These hormones activate the neuronal pathways that trigger synaptic activity. This biochemical mechanism facilitates synaptic plasticity, which in turn, contribute to individual's thoughts, feelings, and behaviors. The abundance of nutrients in the body is important in the synthesis of neurotransmitters and the promotion of critical biochemical processes. Any significant deficiencies can alter synaptic plasticity.

An in-vivo rodent study conducted by Gomez-Pinilla & Ying (2010) showed that a diet rich in omega-3 fatty acids is essential in maintaining synaptic function and plasticity. In contrast, the same

study found that diet high in saturated fat reduced the molecular substances needed to support the cognitive processes, hence, increasing the risk of neurologic dysfunction in animals and humans [7]. The authors argued that, having a good understanding of the molecular components of food, and its effects in the brain function, will be helpful in determining future diet modification strategies. The mesolimbic dopamine (ML-DA) pathway, where the hypothalamus, amygdala and hippocampus are located, is a brain network that is in control of feeding and is associated with the processing of emotions, rewards, and cognition. Addiction to food is said to strongly resemble addiction to drugs of abuse because the ML-DA is the same pathway affecting the susceptibility of an individual to drug addiction [8]. A study conducted by Olsen & Duvauchelle reported that repeated use of opioids and other drugs of abuse create neuroadaptations in the ML-DA pathway that affects processing of natural rewards [9]. Moreover, structural volume alterations in amygdala, hippocampus and hypothalamus brain regions due to opioid use have been reported by Younger and colleagues [10]. These structural and functional alterations may lead to compulsive, pathologic behaviors, such as binge eating, gambling, craving, and impaired control, and tolerance among others [11].

Certain food choices that individuals with OUD prefer, such as high salt, fat, and sugar, are perceived as addictive substances that activate the ML-DA causing the euphorogenic effects. A study by Smith and colleagues showed that both mice and humans with history of opioid dependency had preference for a high salt diet, demonstrating that neuronal pathways modulated by endogenous opioid signaling influence dietary salt consumption [12]. In addition, morphine-exposed rats, on Western-based diet high in saturated fatty acids, were found to be at increased risk of relapse in part due to modification of DA neurotransmission,

specifically increased dopamine transporter (DAT) and dopamine receptor-2 (D2R) immunoreactivity and decreased dopamine receptor -1 (D1R) immunoreactivity in the nucleus accumbens or NAc [13].

Peculiar craving to sweets and high carbohydrates among individuals with OUD was documented as early as the 1980s [14,15]. The desire to consume large quantities of sweet and non-sweet carbohydrate-rich food is associated with increased serotonin levels in the brain [16]. An emerging area of interest is addiction shift (also known as “cross”, “transfer”, or “substitute” addiction). Existing evidence has suggested that individuals with OUD are at a high risk of developing another addiction, such as, food or alcohol. In an animal study, opiates have been found to stimulate appetite for sucrose [17]. Also, consumption of large amounts of sugar-rich food satisfies the “high” individuals with OUD get from drugs [18,19]. The chemical and metabolic compounds found in food serve as triggers to addictive behavior [20]. Foods with high glycemic index, for instance, causes rapid changes in blood glucose, insulin, and hormonal levels which is pharmacokinetically comparable to rapid neurotransmitters changes seen among individuals under the influence of opioids. Animal studies have shown that bingeing on sucrose results in repeated increase of dopamine rather than a gradual decline over time that is typical of natural rewards [21]. Similar increase can be observed in the mu-opioid receptor binding that is akin to drugs of abuse [19]. Examining these similarities in the biopsychology of appetite and substance use disorder can help further our understanding of the causes of malnutrition among individuals with OUDs, its implications to nutrition therapy and substance abuse outcomes. For example, given that many individuals with OUDs are malnourished, it is not surprising that they experience cravings, but it may be difficult for them to differentiate between urges to consume addictive substances and those driven by a need for food, i.e., “addiction transfer” [22]. Food deprivation lowers the threshold for activation of reward pathways, increasing sensitivity to drugs of abuse as well as food, potentially further reinforcing consumption of either [23-25]. Nutrient deficiencies may also contribute to cravings or at least encourage drug seeking, as nutrient depleted animals seek novel reinforcing experiences, mediated by brain dopamine activation, drink more alcohol and prefer alcohol-paired flavors [26-29].

To remedy the nutritional deficiency and brain abnormalities in OUDs, we propose the following strategies:

**1. Nutrient Supplementation:** It has been suggested by Jadavji and colleagues that B-vitamins and choline supplementation increases neuroplasticity and recovery after stroke [30]. B-vitamin supplementation is particularly useful in decreasing the high concentrations of homocysteine, which is typically found in opium-addicted individuals and is associated with increased risk of dementia and cognitive impairment [31-33]. Based on this finding, we suggest that providing supplementation will increase brain neuroplasticity and recovery that will aid individuals in the process of overcoming opioid use disorder.

**2. A Multinutrient Supplementation Diet:** According to the stroke literature, a specific dietary intervention can restore brain structure and function after ischemic stroke [34]. More specifically, mice on the multicomponent diet showed decreased neuroinflammation, improved functional and structural connectivity, beneficial effect on cerebral blood flow (CBF), and improved motor function after ischemic stroke. Fortasyn, a dietary approach comprising docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA),

uridine, choline, phospholipids, folic acid, vitamins B12, B6, C, and E, and selenium, counteracted neuroinflammation and impairments of cerebral structural plus functional connectivity, CBF, and motor function. There is also evidence that omega-3 polyunsaturated fatty acids (PUFA) such as alpha linolenic acid (ALA), EPA, and DHA may be useful in providing neural protection, especially of the hippocampus, in individuals suffering from acute neuronal injury, stroke, and other neuropsychiatric disorders [35]. Accordingly, we propose that Fortasyn, a multinutrient supplementation diet, can be recommended to recovering opioid users to increase sensitivity to natural reward and to avoid binge eating of fatty and sugary food, craving, and impaired control.

**3. Ketogenic Diet:** The ketogenic, a low-carbohydrate and a high protein and fat, diet has been shown to have unique properties that make it a more suitable cerebral fuel under various neuropathological conditions (e.g., starvation, ischemia, and traumatic brain injury (TBI) [36]. We propose that the ketogenic diet can be introduced for individuals recovering from OUD as this diet has therapeutic potential in improving cognitive deficits as experienced by OUDs.

**4. Mediterranean Diet:** One diet in particular, the Mediterranean Diet (MeDi), characterized by high intake of fruits, vegetables, cereals, fish, nuts and olive oil, has received particular attention in the literature. The benefits of adherence to this type of diet have been evidenced in both epidemiological studies and clinical trials and include lower incidence of dementia and Alzheimer’s Disease and reduced risk for developing cancer, metabolic syndrome and vascular disease [37]. We propose that this kind of diet can be introduced for individuals recovering from OUD as this diet can improve cognitive function in OUDs.

**5. Mindfulness Meditation:** Mindfulness-based stress reduction (MBSR) has been shown to improve quality of life of individuals with gastrointestinal disorders by decreasing flare-ups and symptom severity [38,39]. Mindfulness interventions, such as mindful eating, activate the parasympathetic nervous system to optimize digestive function by targeting stress, which is responsible for GI dysfunction by offsetting biological homeostasis and mindfulness [40]. These interventions have also been successful in quelling food cravings, particularly of sweets and salty junk food, in obese individuals; and thus, decreasing consumption of these foods in this population [41,42]. We propose that mindfulness mediation can be incorporated into treatment of OUDs to help combat the nutritional deficiencies OUDs experience, decrease cravings for sweets and salty food, and thus decrease risk for relapse following recovery.

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#### Disclosure Statement

The authors report no relevant disclosures.

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