

NUTRIENT AND FOOD COMPONENT SUPPLEMENTATION
FOR SUBSTANCE USE DISORDER RECOVERY:
A SYSTEMATIC REVIEW

by

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LIST OF ABBREVIATIONS

Abbreviation	Description
SUD	Substance Use Disorder
MNT	Medical Nutrition Therapy
PRISMA	Preferred Reporting Items for Systematic Reviews
PICO	Population, Intervention, Control, Outcome
NAC	N-acetylcysteine
SADD	Short Alcohol Dependence Data
OCDS	Obsessive Compulsive Drinking Scale
CPP	Conditioned Place Preference

ABSTRACT

The recovery stage of addiction is a challenging phase characterized by withdrawal symptoms, cravings, and a 40-60% risk for relapse. Nutritional psychiatry is an emerging field of medicine focused on optimizing mental and physical function by providing essential nutrients, treating deficiencies, and using food as medicine. Nutritional intervention has the potential to enhance recovery success by providing the brain with needed nutrients to heal and by reducing withdrawal and craving symptoms. To this end, we conducted a systematic review of preclinical and clinical nutrient and food-derived interventions showing evidence of reducing relapse or craving. Separate searches were conducted utilizing the SCOPUS and the PubMed databases. After eliminating duplicates, the combined search yielded 9,452 peer-reviewed studies. The original search ended on February 23, 2018 and a final search through PubMed and Scopus was performed on June 28, 2018, yielding 30 applicable studies. Articles were assessed by three investigators for inclusion using the following criteria: (1) Clinical or preclinical studies of any diet, nutrient, or food component including vitamins, minerals, amino acids, and fatty acids (or any miscellaneous food-based supplement); (2) Studies of any drug of abuse including alcohol, nicotine, and cannabis; (3) Randomized controlled trials; (4) Studies during abstinence with the outcome measure as reduction of craving or relapse. Studies including participants currently undergoing Medication-Assisted Treatment (e.g. methadone and buprenorphine) or smoking cessation (nicotine or cannabis) studies were also included. This systematic review encompasses trials that include male and female subjects, as well as individuals with different ethnic backgrounds to provide a subject pool representative of the population. Results of the review show that one amino acid, polyunsaturated fats, and one mineral may significantly reduce craving

and/or withdrawal symptoms related to addiction. For each reviewed food component, possible mechanisms of action are explored, such as neurotransmitter regulation and gene regulation. Recommendations include research of the food components' mechanisms of action in relieving symptoms of SUD and possible synergistic effects between food components.

I. INTRODUCTION

Substance Use Disorder (SUD) is a disease of the brain that results in persistent seeking and taking of drugs despite negative consequences to health, social, occupational, and societal function.¹ The United States has experienced a doubling of drug related deaths in the last decade.² In 2017, over 72,000 people in the United States died of drug overdose.³ Currently, the national cost of abuse of illicit drugs and prescription opioids is estimated to have reached a staggering \$271.5 billion dollars annually in related health care costs, loss of productivity, and crime.² Drug use results in both short and long term negative effects in the body. Short term effects can include increased heart rate, psychosis, stroke, overdose, and death. Long term drug use can result in disease of vital organs, contraction of human immunodeficiency virus or hepatitis C through shared paraphernalia, and mental illness.⁴ In the United States, 40-60% of individuals who attempt abstinence from drugs of abuse will experience relapse.⁵ To this end, there is an urgent need for development of new interventions to prevent drug overdose and enhance recovery efforts.

Substance Use Disorder

Substance Use Disorder is characterized by the inability to control intake of drugs and physical or emotional withdrawal resulting from drug cessation.¹ Currently there is not a complete understanding of the mechanisms surrounding SUD. However, it is known that SUD comprises of both neurological and psychological aspects. Koob and Moal⁶ developed a depiction of the addiction cycle by combining aspects of compulsivity and impulse control disorders (Figure 1). Once recreational drug use transitions into dependence, the cycle of binge/intoxication, withdrawal/negative effect, and

preoccupation/anticipation begins. Each factor in the addiction cycle coincides with acute and chronic neurological adaptations in the reward system, specifically the mesocorticolimbic pathway.⁷⁻¹⁴

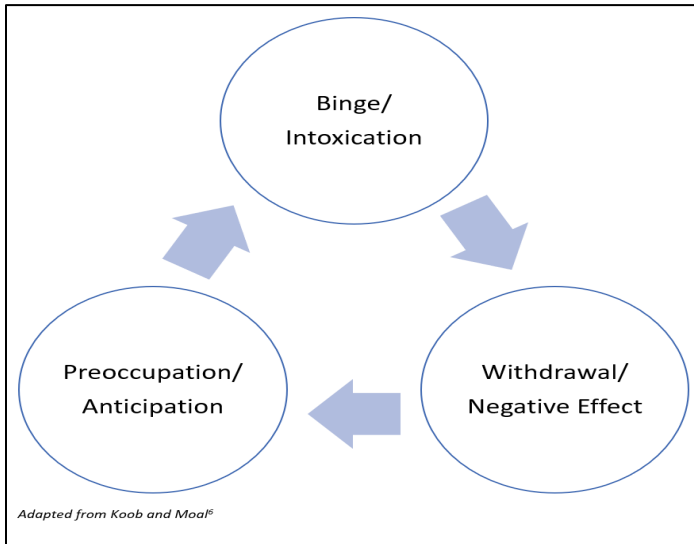


Figure 1. The Cycle of Addiction

The mesocorticolimbic pathway is comprised of the mesocortical and limbic systems of the brain. The mesocortical system consists of the ventral tegmentum area, a key player in motivation and the reward pathway, and the prefrontal cortex which is responsible for executive control. The limbic pathway is comprised of the hippocampus, nucleus accumbens, amygdala, thalamus, and hypothalamus, and is responsible for emotion, memory, and relaying information to other parts of the brain.¹⁵ Together, the mesocortical and limbic systems award the act of drug taking with a value, encoding the hedonic effect achieved with each use. Drugs of abuse produce hedonic effects by binding to one or more of three opioid receptor types; mu, delta, and kappa (Figure 2).^{16,17} Common drugs of abuse, such as morphine and heroin, have a high affinity for the μ -opioid receptor, in particular. The antagonistic activation of the μ -opioid receptor by these substances results in pain relief, euphoria, and potential dependence.¹⁸ Alcohol also

affects the opioid system. Specifically, Mitchell et al.¹⁹ concluded that endogenous opioids are released upon intake of ethanol, and subsequently attach to opioid receptors, providing pleasurable feedback associated with alcohol intake.

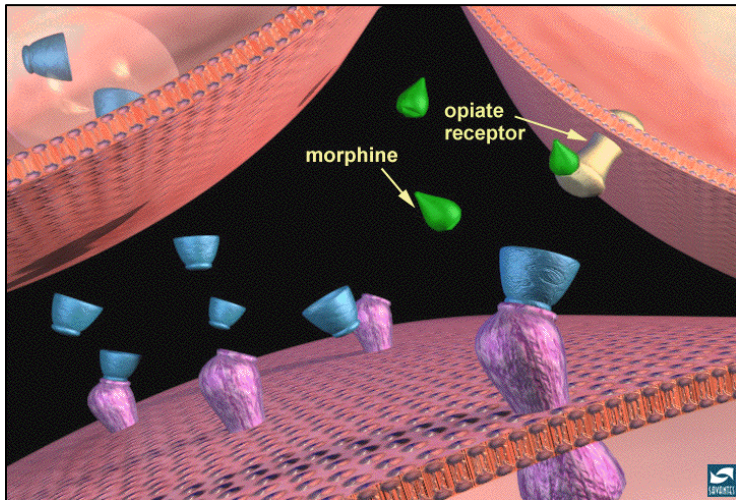


Figure 2. Opioid binding to opioid receptor. National Institute on Drug Abuse, 2007.

Further, drugs of abuse are more powerful than natural reinforcers, such as food or sex.²⁰ Pleasurable events or substances, called “positive reinforcers” result in a dopamine release in the nucleus accumbens and prefrontal cortex.²¹ Extreme positive reinforcers, i.e. drugs of abuse, result in the attachment of dopamine to dopamine receptors, which is a factor responsible for pleasurable feelings associated with drug intake. These positive feelings caused by drug intake further fuel incentive salience in situations involving drug cues, increasing the risk for relapse.²² Further, as the cycle of addiction continues, negative reinforcement of dependence occurs once undesirable effects of withdrawal takes place, causing a chronic cycle of drug taking, withdrawal, and relapse.^{6,14}

Treatment

The first step of SUD recovery is detoxification to remove drugs of abuse from the body. However, because SUD is a chronic disease, detoxification alone will likely not prevent an individual from using drugs again. Substance Use Disorder recovery requires a well-rounded approach that addresses many needs of an individual suffering from SUD. Many treatment approaches can be used in either out-patient programs or in rehabilitation facilities.²³

Several types of therapies can be utilized to combat SUD. Examples of these therapies include motivational enhancement therapy, cognitive behavioral therapy, and 12-step facilitation therapy.^{23–26} Motivational enhancement therapy is generally utilized to assist with the cessation of substances such as nicotine, alcohol, and cannabis. With this method, motivational interviewing is used to create patient-generated motivation and proposals to quit using addictive substances.²⁴ Cognitive behavioral therapy is used to change the associations and behaviors individuals have with drugs of abuse, as well as develop strategies to identify and manage situations where risk of relapse is high.²⁵ Further, twelve-step facilitation therapy is often in a group setting to provide support and guidance to its members. The 12-step program typically consists of three main concepts; (1) accepting that substance use disorder is a life-long struggle and that abstinence is the key to recovery, (2) surrendering to the guidance of the 12-step program and a “higher power”, and (3) retaining active participation in 12-step groups and events.²⁶ In addition to these therapies, it is important to address and treat any co-existing mental illnesses present in an individual.

Medication-assisted treatment (MAT) is a commonly used method to treat SUD because it can be effective at reducing cravings and regaining brain function during recovery.²⁷ Methadone is an opioid receptor agonist commonly used to treat opioid dependence. Because methadone itself is an opioid, there is a risk for dependence and abuse with this treatment method.²⁸ Individuals prescribed methadone must receive the drug under the supervision of a physician participating in an Opioid Treatment Program that is certified by the Substance Abuse and Mental Health Services Administration.²⁸ Naltrexone, another SUD treatment, is an antagonistic drug that blocks the hedonic effects of opioids and alcohol.²⁹ While naltrexone has a low risk of abuse, individuals using naltrexone for MAT may develop a lower tolerance to opioids which may increase risk of overdose upon relapse.²⁹ Abstinence from opioids and the blocking of the μ -opioid receptors via naltrexone allows opioid receptors to regain baseline sensitivity to opioids. In addition, once naltrexone dosing is stopped, the μ -opioid receptors are quickly unblocked. Individuals in relapse often consume opioid amounts they used prior to treatment, unknowingly taking a much higher dose required for their new lowered tolerance and therefore risking overdose.³⁰ Another opioid-dependency treatment, buprenorphine, is a partial agonist to the opioid receptor, providing a small level of euphoria.³¹ The hedonic properties of buprenorphine can increase with increasing doses to a certain extent but will then reach a steady state even with additional doses. Buprenorphine can be prescribed in a doctor's office and has a low risk of abuse because the euphoric properties are minimal in comparison to opioids.³¹ For alcohol dependence specifically, disulfiram and acamprosate both reduce drinking tendency via different mechanisms. Disulfiram inhibits normal alcohol metabolism causing severe reactions

such as vomiting, headaches, trouble breathing, increased heart rate, and anxiety. The mechanism of action for acamprosate is unknown but the drug has been shown to reduce the desire to drink alcohol in alcohol-dependency.

Under federal law, outpatient treatment centers are required to provide counseling to MAT participants, owing to the synergy of simultaneous use of these modalities increasing the chance of recovery.²⁹ While the use of MAT and counseling can be useful during recovery efforts, the risk for abuse of recovery medications, relapse, and overdose during MAT still remains high. In addition, there are no FDA-approved MATs for recovery from stimulants (e.g. cocaine or methamphetamine). To this end, there is still a need for additional treatments to enhance outcomes for long-term SUD recovery and further reduce relapse rates.

Medical Nutrition Therapy

Medical nutrition therapy (MNT) provides an individualized nutrition program in clinical settings for the management of disease. Nutrition therapy has been used to successfully treat bodily diseases such as diabetes and cardiovascular disease for some time. Nutrition therapy has also been used to treat neurologic disease. For example, the ketogenic diet was developed in the 1920s and has been used since to treat epilepsy.³² New evidence also supports nutrition therapy for the treatment of other neurological disorders such as ADHD³³ and Alzheimer's disease.³⁴ An emerging branch of nutrition therapy addressing psychiatric disorders, termed nutritional psychiatry, has provided evidence supporting nutrient or diet interventions for depression³⁵ and psychosis.³⁶ Nutritional psychiatry focuses on providing nutrients or altering diets to enhance brain

and body function with the goal of reducing symptoms of common mood disorders.³⁷ To this end, nutrition therapy also can and should be applied to drug dependence. Most nutrition related research in the area of SUD has focused on nutrient deficiencies resulting from drug abuse (for example, see Jeynes & Gibson³⁸). For example, Ross et al.³⁹ found that 21% individuals participating in drug detoxification were deficient in vitamin A, 8% were vitamin C deficient, and 18% were deficient in iron. In addition, individuals with alcohol dependence are commonly deficient in B vitamins and vitamin A due to reduced intake of food and the effects alcohol has on nutrient absorption and metabolism.⁴⁰ Alcoholic thiamine deficiency can affect up to 80% of individuals with alcoholism and can lead to neurological deficits and psychosis known as Wernicke-Korsakoff syndrome.^{41,42} It is important to understand these deficiencies and their impact on the mechanisms of addiction. It is equally important to correct these deficiencies in rehabilitation with addiction nutrition. However, once a person is in rehabilitation and has transitioned to a more healthful diet, these deficiencies are presumably corrected. Nutritional support is then needed during abstinence to reduce the recurring cravings and the characteristic chronic relapse of recovery.⁴³ This chronic relapse related to drug addiction is due, in part, to poorly functioning reward mechanisms in the dopaminergic mesocorticolimbic pathway.¹⁴ A nutrient or food component supplementation regimen to support and/or restore these processes has the potential to improve brain function, thereby further promoting abstinence and reducing risk of relapse.

There are numerous preclinical and clinical trials published investigating the role of individual nutrients in reducing cravings or relapse. To our knowledge, no one has compiled these studies in order to formulate an evidence-based treatment program. This

systematic review aims to compile such evidence supporting nutrient or food component supplementation to reduce cravings and relapse in drug dependent populations throughout recovery.

II. METHODS

We conducted a systematic search following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in order to provide transparency through our search and selection process.⁴⁴ We searched for relevant articles using the electronic databases PubMed and Scopus. The Population, Intervention, Control, and Outcome (PICO) method was used to help define our question and determine our search terms.⁴⁵ The search terms are reported in Table 1 and were used for both online databases. One difference between the search terms for each database was the PubMed search also contained “NOT “food addiction””.

Table 1. PICO (Population, Intervention, Comparator, Outcome)

Population	Intervention			Comparator	Outcome
Addict	Vitamin A	Manganese	Threonine	(Not appropriate for search)	Relapse
Alcoholic	Retinol	Copper	Tryptophan		Craving
Addiction	Carotenoid	Iodine	Tyrosine		Abstinence
Drug abuse	Thiamine	Chromium	Valine		
Methamphetamine	Riboflavin	Molybdenum	Fat		
Cocaine	Niacin	Selenium	Saturated fat		
Heroin	Pantothenic acid	Cobalt	Unsaturated fat		
Morphine	Pyridoxine	Protein	Polyunsaturated		
Opioid	Biotin	Amino acid	Cholesterol		
Opiate	Folate	Alanine	Omega 3		
Alcohol	Vitamin B12	Arginine	DHA		
Nicotine	Vitamin C	Asparagine	Docosahexaenoic acid		
Cannabis	Vitamin D	Aspartic acid	EPA		
Marijuana	Vitamin E	Cysteine	Eicosapentaenoic acid		
	Tocopherols	Glutamic acid	Omega 6		
	Tocotrienols	Glutamine	Phosphatidylserine		
	Vitamin K	Glycine	Phosphatidylcholine		
	Phylloquinone	Histidine	Fish oil		
	Menaquinones	Hydroxyproline	Lecithin		
	Potassium	Isoleucine	Sphingolipid		
	Chlorine	Leucine	Carbohydrate		
	Sodium	Lysine	High protein		
	Calcium	Methionine	Ketogenic		
	Phosphorous	Phenylalanine	High fat		
	Magnesium	Proline	Low fat		
	Iron	Pyroglutamate	Fatty acids		
	Zinc	Serine			

Additional articles were found through selecting references in related review papers. Articles were screened by three investigators to determine if they fit the inclusion criteria. The inclusion criteria were: (1) effects of diets including ketogenic, high-fat, and low-fat or nutrients, including vitamins, minerals, amino acids, and fatty acids (or any miscellaneous food-based supplement), (2) clinical or preclinical studies, (3) randomized controlled trials, (4) studies with the outcome measure of craving, relapse, or abstinence, and (5) studies including participants currently undergoing MAT (e.g. Methadone and Buprenorphine). Articles were excluded if they met the following: (1) review papers; however, references listed in review papers were screened to find more primary data sources, (2) studies with no specific nutrient/diet intervention, (3) studies examining herbal medicine or a pharmaceutical, (4) studies with participants still actively consuming drugs of abuse (except alcohol, nicotine, and cannabis). In addition, we excluded any articles not available in English. The original search ended on February 23, 2018 and a final search through PubMed and Scopus was performed on June 28, 2018. The PRISMA flow diagram shown in Figure 3 depicts the process for which studies were chosen for the systematic review.⁴⁴ Each food category assessed was analyzed for a level of evidence utilizing a chart adapted from the Centers of Disease Control Continuum of Evidence Effectiveness as seen in Figure 4.⁴⁶ Terms defined in the Levels of Evidence Figure are as follows: “risk factors” include withdrawal symptoms and anxiety; and “other potential risk factors” include conditioned place preference.

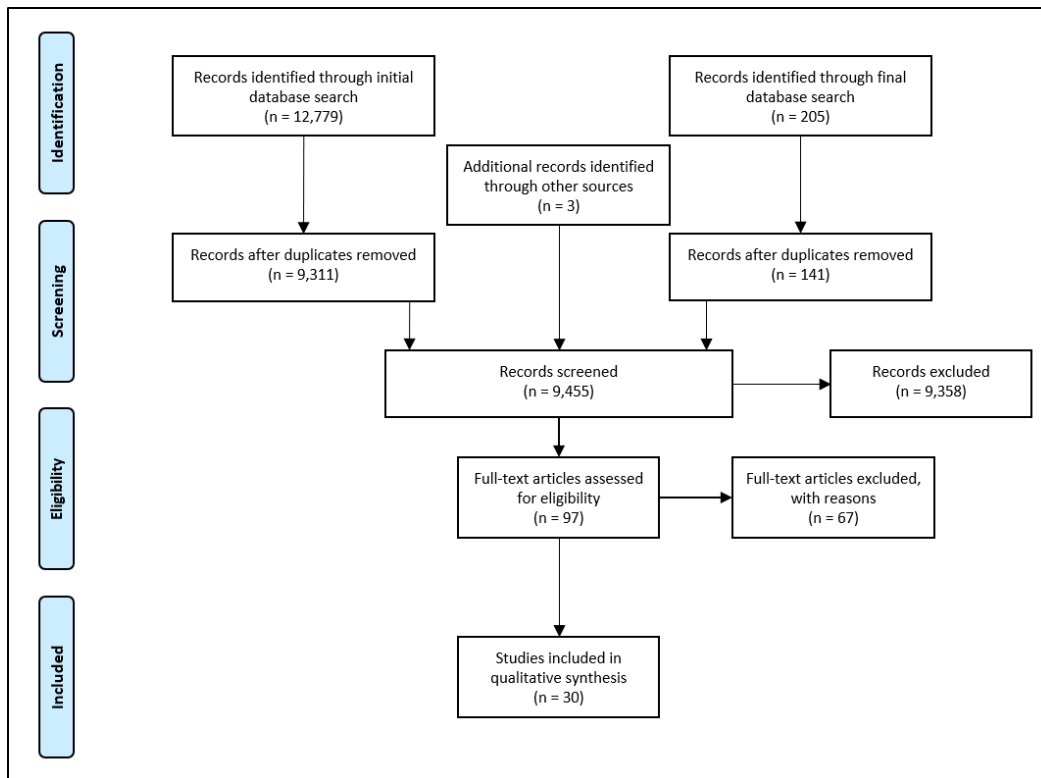


Figure 3. PRISMA Flowchart showing article selection phases throughout the search process.

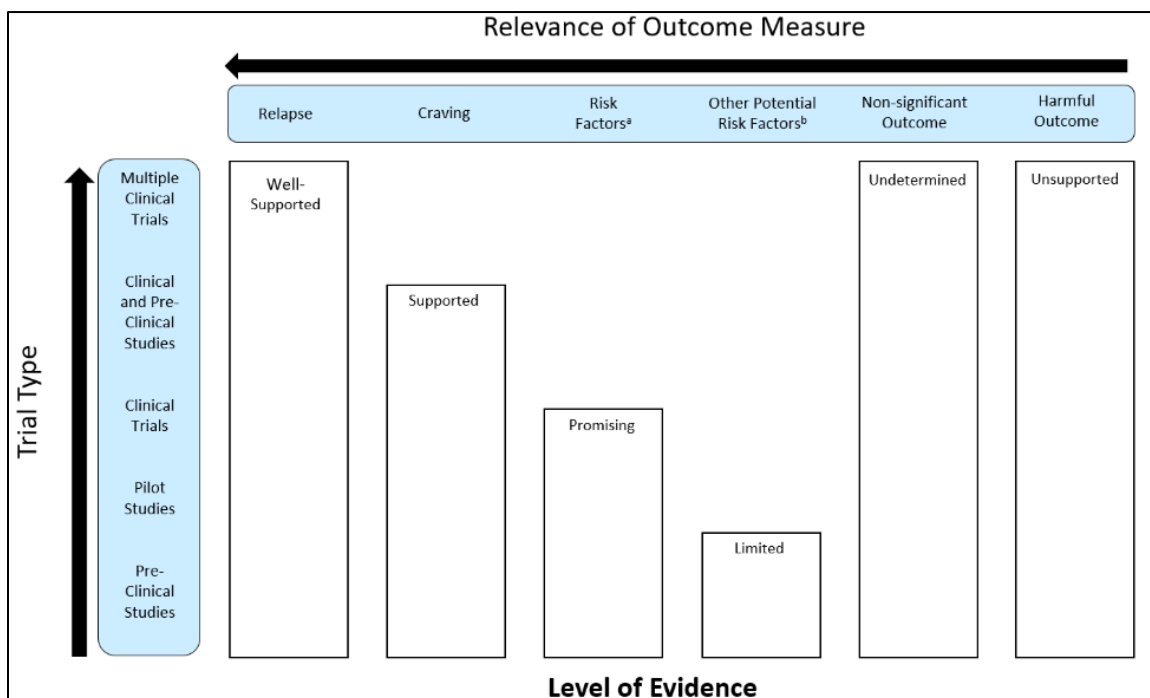


Figure 4. Level of Evidence. ^aRisk factors include withdrawal symptoms and anxiety. ^bOther potential risk factors include conditioned place preference.

III. RESULTS

The initial search generated a total of 9,311 articles (Figure 3) after duplicates were deleted. The second and final search generated an additional 141 articles after duplicates were removed. From the original searches, articles with a title or abstract that were clearly not relevant to our search as well as articles not in English were excluded (n=9,358). From the remaining 97 full-text articles, a total of 30 were selected based on relevancy to inclusion criteria. The resulting food components or nutrients of significance include N-acetylcysteine, omega-3 fatty acids, and magnesium (Table 2).

Table 2. Positive Result Studies

	Nutrient/Food Component	Positive Results	Level of Evidence	Possible Mechanisms
Evidence from systematic review	N-acetylcysteine	Cocaine ¹⁷ Nicotine ^{18,19} Cannabis ²⁰ Alcohol ²¹	Well- supported	Maintenance of extrasynaptic glutamate concentrations. ^{18,46-48}
	Omega-3 Fatty Acids	Alcohol ^{32,33}	Supported	Regulation of D2R in nucleus accumbens. ⁶⁸
	Magnesium	Opioid ⁴²	Promising	Inhibition of calcium-dependent dopamine release. ⁷⁷ Inhibition of nitric oxide synthase. ⁷⁹
Additional evidence	Vitamin D3	Amphetamine ⁸⁶	n/a	Increased mRNA expression of GDNF. ⁸⁴ Upregulation of D2R expression in the nucleus accumbens. ⁸⁶
	Calcium	Opioid ⁹⁰	n/a	Regulation of dopamine release via calcium dependent dopamine channels. ^{88,89}

Amino Acids

Amino Acid Supplementation

N-acetylcysteine (NAC) is the supplemental form of the non-essential amino acid, cysteine. Two pre-clinical and five clinical studies were found using NAC to treat SUD during recovery.^{9,47-51} In a rodent model, Amen et al.⁴⁷ trained rats to self-administer cocaine by lever press to trigger an infusion of cocaine (0.5 mg/kg/200µl), intravenously. The rats were administered a daily NAC (60 mg/kg) intraperitoneal injection or no NAC to serve as a control during cocaine use and reinstatement periods. Afterwards, an extinction phase occurred by replacing the cocaine associated with a lever press with saline only. The extinction phase continued until lever presses averaged under 10 presses over at least three of four sessions. Rats were then reinstated to self-administer cocaine via lever press during two sessions, with one week between sessions. Initially and during the first reinstatement test, NAC did not reduce reinstatement of cocaine seeking in rats ($p = 0.525$). However, during the second reinstatement test, lever responses decreased significantly ($p = 0.023$) in rats given daily NAC supplementation. Thus, in this study, NAC supplementation, though not immediately effective, showed promise as a supplement. In another study,⁹ two groups of male Wistar rats ($n=75$) were trained to associate specific cues with the availability of reward in the form of nicotine (0.03 mg/kg), saccharin (100 µl, 50/1 solution in H₂O), or no reward via lever push. Rats proceeded through self-administration, extinction, and reinstatement training. Results revealed that doses of 30 and 60 mg/kg NAC did not have effect on number of lever presses ($p > 0.05$). Furthermore, administration of NAC (100 mg/kg, IP) did not reduce saccharin seeking attempts in the reinstatement phase ($p > 0.05$). However, supplementation with 100 mg/kg NAC was effective at reducing the amount of lever

presses for nicotine seeking ($p < 0.05$). The results of this study suggest that in some cases/doses, NAC may reduce drug seeking activity.

In a clinical arm of the Amen study,⁴⁷ cocaine-dependent participants ($n=6$) who were 8-48 hours abstinent received cocaine (20 mg/70 kg/60 s) using intravenous administration. Assessment of participants' high, rush, and craving were assessed after each of three sessions via visual analog scale. Participants were given oral doses of NAC (400 or 800 mg/dose; $n=4$) or baclofen (20 mg/dose; $n=4$), a GABA B receptor agonist used for craving reduction in substance abuse disorder, 1 to 2 times (depending on when participants finished pre-NAC administration test session) daily on days 1 (pre-drug session), 3 times daily on days 2 and 3, and 4 (post-drug session). The tests given pre- and post-NAC administration included 3 sessions of visual stimuli showing neutral videos or a trigger video depicting drug-use. After the 3rd session, cocaine (20 mg/70 kg) was administered. While results showed no effect of cocaine's reinforcing ability or hedonic properties ("high" and "rush") in the NAC group ($p = 0.433$), feelings of drug craving were significantly ($p = 0.001$) reduced in the NAC group compared to the baclofen group. Additionally, a pilot study⁴⁸ assessed NAC in therapy resistant participants to treat nicotine/tobacco dependence. Baseline and endpoint levels of daily cigarettes smoked, exhaled CO, and cessation rates were assessed. Participants were randomly assigned 3 g/day oral NAC ($n=17$) or placebo ($n=17$) for 12 weeks. Cigarettes smoked per day significantly ($p = 0.006$) decreased in the NAC group, as well as exhaled CO levels ($p < 0.001$). Compared to 21.4% cessation in the placebo group, there was significantly ($p = 0.006$) greater cessation (47.1%) in the NAC group. Furthermore, Gray et al.⁴⁹ assessed the efficacy of NAC to encourage abstinence in cannabis dependent

adolescents (n=116). In a double-blind, placebo-controlled trial, NAC (1200 mg) or placebo was administered daily to participants in combination with cessation counseling. Participants receiving NAC were nearly twice as likely to submit a negative urine test over the course of the 8-week study ($p = 0.029$). A second assessment by Squeglia et al.⁵⁰ of the same study examined alcohol drinking habits of the participants. Data showed that participants who reduced cannabis use did not replace cannabis use with alcohol intake. Furthermore, the NAC group with higher rates of cannabis negative urine tests, also reported lower accounts of alcohol use in comparison with the placebo group ($p = 0.016$).

In contrast to the positive studies, a clinical study from LaRowe et al.⁵¹ exploring the efficacy of NAC supplementation in reducing cocaine use found no significant results regarding NAC supplementation and reduction of craving, withdrawal, or abstinence. Over 8 weeks, cocaine-dependent participants were supplemented with NAC. Participants were randomly assigned to 3 groups: 1) NAC (1,200 mg); 2) NAC (2,400 mg); or 3) placebo. Self-reports of cocaine use and urine tests to detect use were performed up to 3 times per week for the duration of the study. The Brief Substance Craving Scale (BSCS) was administered weekly to assess craving. Overall, results showed no significant difference in abstinence rates, craving, or withdrawal symptoms for any group ($p > 0.05$).

Other amino acids that have been explored preclinically are L-theanine, kynurenic acid, serine, D-cycloserine, and sarcosine. L-theanine, while not a nutrient, is a non-protein amino acid that is contributed to diet primarily from tea.⁵² In a pre-clinical study, Wise et al.⁵³ assessed the effect of L-theanine on withdrawal symptoms in morphine dependent monkeys (n=24). Rhesus monkeys were administered L-theanine (1, 4, 8

mg/kg), morphine (4 mg/kg; control), or vehicle control (sterile water, 1 mL/kg) after being 14 to 15 hours abstinent. Withdrawal symptoms were assessed at 30, 60, 90, 120, and 150 minutes, and categorized into absence or presence of withdrawal symptoms. Monkeys who received 8 mg/kg of L-theanine exhibited a significant ($p < 0.05$) reduction in withdrawal symptoms as compared to vehicle control group at the 30- and 60-minute assessment. Monkeys who received 4 mg/kg or 8 mg/kg also showed a significant ($p < 0.05$) decrease in withdrawal symptoms as compared to controls at the 90-, 120-, and 150- minute assessments.⁵³

Rasmussen et al.⁵⁴ examined the effects of kynurenic acid, a metabolite of L-tryptophan and an excitatory amino acid receptor antagonist, on morphine withdrawal. After induction of opiate dependence, male Sprague-Dawley rats were inoculated with kynurenic acid (10, 100, or 500 mg/kg) subcutaneously, kynurenic acid (0.1 μ mol or 0.25 μ mol) intracerebroventricular injection, or saline (control). Withdrawal was assessed on scoring of incidents (including irritability, jumping, wet dog shakes, writhing, and head bobbing) and behaviors (teeth chattering, lacrimation, piloerection, ptosis, salivation, chewing, and diarrhea). Withdrawal from morphine was induced by administering naltrexone HCl (10 mg/kg) 15 minutes after kynurenic acid injection. Significant reduction in wet dog shakes ($p = 0.044$) and lacrimation ($p = 0.001$) was seen in rats who received 0.25 μ mol kynurenic acid. There was also a significant reduction in the 500 mg/kg group for ptosis ($p = 0.001$), lacrimation ($p = 0.006$), and saliva ($p = 0.029$) compared to both the control group and groups receiving 10 and 100 mg/kg kynurenic acid subcutaneously.

Yang et al.⁵⁵ compared the effectiveness sarcosine, D-serine, and D-cycloserine to reduce or extinguish cocaine conditioned place preference (CPP). Sarcosine is an intermediate of the amino acid, glycine, formation.⁵⁶ Both D-serine and D-cycloserine are supplemental forms of amino acids that act as agonists to the N-methyl-d-aspartic acid receptor in the brain.^{57,58} Place preference was tested by placing male C57BL/6NJ mice (n= 166) in a randomly chosen compartment and allowing them to freely explore the two compartments for 15 minutes. The mice received D-cycloserine (30 mg/kg), sarcosine (300 or 600 mg/kg), D-serine (300 or 600 mg/kg), or saline (control) after each cocaine-free test. Twenty-one mice were excluded from the study by displaying a significant preference for a particular compartment. The mice were then administered cocaine HCl (10 mg/kg, IP) while sequestered in the lesser-preferred compartment for 30 minutes for the cocaine-induced CPP (Test 1 or T1). Eight hours later the mice received an equivalent dose of saline (control) and were sequestered in their more-preferred compartment. The saline treatment was repeated for an additional two days. After the last saline treatment, drug-free mice were placed in the center compartment and were allowed to enter any compartment to assess cocaine seeking behaviors. Mice spending 20% or more of the allotted time in the center compartment were excluded. The CPP test was repeated five times (T1-T5) over five days. Maintenance of cocaine-induced condition place preference test (priming test) was assessed after T5 by administration of cocaine (10 mg/kg) prior to release into compartments. Mice treated with D-cycloserine exhibited a significant ($p < 0.0001$) decrease in cocaine-induced CPP on T2 through T5. Sarcosine (300 mg/kg and 600 mg/kg) and D-serine (300 mg/kg and 600 mg/kg) both significantly ($p < 0.001$) reduced cocaine-induced CPP on T4 and T5.

Jukic et al.⁵⁹ provided an amino acid supplement to participants in a randomized, double-blind, placebo-controlled trial. Alcohol-dependent patients (n= 20) who were entering a detoxification program were randomly assigned to two groups; (1) daily supplementation with D/L-phenylalanine (300 mg), L-glutamine (150 mg), and L-5-hydroxytryptophan (5 mg) or (2) placebo group. The Symptom Checklist-90-Revised test (SCL-90-R) was used to evaluate psychiatric symptoms including somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. The SCL-90-R test was administered at the initiation of study and at the end of 40 days. The results revealed supplementation with D/L-phenylalanine, L-glutamine, and L-5-hydroxytryptophan significantly reduced all evaluated SCL-90-R factors ($p < 0.05$), excluding anxiety.

Tryptophan is an essential amino acid that must be obtained from the diet, and is a precursor to the neurotransmitter, serotonin.⁶⁰ Tryptophan supplementation in combination with a high carbohydrate diet and group therapy were assessed for the effectiveness of enhancing smoking cessation by Bowen et. al.⁶¹ The high-carbohydrate diet consisted of a 7:1 ratio of carbohydrate to protein, while the low-carbohydrate diet consisted of a 1:1 ratio of carbohydrate to protein. Both diets matched the average caloric intake of each individual as assessed by a dietician prior to the study. Participants were randomly assigned to either a tryptophan supplement (50mg/kg/day) combined with a high carb diet (n=16), or a placebo supplement combined with a low carbohydrate diet (n=15). Both groups received group therapy to support smoking cessation. After two weeks, participants who received tryptophan supplementation and followed a high carbohydrate diet smoked fewer cigarettes than those in the placebo group. A significant

($p < 0.001$) reduction of anxiety symptoms were reported in the tryptophan group, as well. This study suggests that increased intake of tryptophan may reduce feelings of anxiety and reduce smoking behavior.

Amino Acid Depletion

Petrakis et al.⁶² examined whether tryptophan depletion could reduce trigger induced alcohol craving symptoms in alcoholics ($n=16$) during recovery. In a double-blind, placebo-controlled study to assess baseline craving levels via craving questionnaire, participants were exposed to a trigger in the form of smelling but not consuming an alcoholic drink on the first test day. On the second and third test days, participants were given a tryptophan-deplete drink or tryptophan-containing drink (placebo) to consume 5 hours before trigger exposure. Following trigger exposure, the participants complete a craving questionnaire. Results showed that tryptophan depletion had no effect in reducing cravings in alcohol dependent participants. In another tryptophan depletion trial, Wedekind et al.⁶³ assessed the efficacy of tryptophan depletion in treating craving and psychological symptoms in alcohol dependent males ($n=25$). Participants' psychological status was examined by Montgomery-Asberg Depression Rating Scale (MADRS), State-Trait Anxiety Scale, and the Hamilton Anxiety Scale, and substance craving by visual analog scale at baseline and endpoint measures. Participants were randomly assigned to receive a tryptophan-deplete or tryptophan-rich amino acid drink (2.3 g tryptophan per drink) 24 hours after following a low-tryptophan diet. The average daily tryptophan intake from the diet is 900-1000 mg for adults.⁶⁴ In a crossover design, the same participants received the alternate drink after the low tryptophan diet one week later. While there was no significant ($p > 0.05$) difference in craving symptoms

between tryptophan-deplete and tryptophan-rich groups, tryptophan depletion significantly increased feelings of depression ($p < 0.01$) by the end of the study of the weeklong study. This study suggests that tryptophan depletion may have deleterious effects on mood.

Perugini et al.⁶⁵ addressed tryptophan depletion in a randomized, double-blind, placebo-controlled trial consisting of male participants ($n=18$) who were nicotine dependent. Data of self-reported mood and withdrawal symptoms assessed via questionnaire were collected prior to smoking cessation, 5 hours after cessation, after a faux smoking session, and after smoking a cigarette. After the 5-hour cessation period, participants were given either a tryptophan-deplete or an amino acid balanced drink (placebo). These methods were completed again in a crossover design after a minimum of three days, where participants received the amino acid drink they did not receive in the first session. Results of this study revealed that tryptophan depletion had no significant effect on withdrawal symptoms or self-reported mood ($p > 0.05$). Results of this study suggest that tryptophan depletion is not effective in alleviating withdrawal symptoms in nicotine dependence.

In contrast to tryptophan depletion, a study investigation the effects of phenylalanine and tyrosine depletion on smoking cessation yielded positive results. Venugopalan et al.⁶⁶ assessed three groups of abstinent cigarette smokers ($n=47$), on their motivation to smoke when phenylalanine and tyrosine deplete. The three groups were categorized into: (1) participants who smoked no more than five cigarettes per day and had been smoking less than a year, (2) participants who smoked no more than five cigarettes per day and had been smoking at least three years and, (3) participants who

smoked at least 10 cigarettes per day and had been smoking for at least five years. In this double-blind study, participants were randomly assigned and administered a phenylalanine and tyrosine deplete drink or an amino acid balanced mixture (placebo) at the beginning of each test day. In a crossover design, two tests were conducted three days apart where participants received the alternate amino acid drink on the second test day. A visual analog scale was used to assess the participants feelings in relation to smoking and a craving questionnaire was administered; (1) immediately after drink administration, (2) 4 hours after drink administration, and (3), and at the end of the test day. The tests included triggers such as holding a cigarette shaped item, holding but not smoking a lit cigarette, and the chance to earn mini cigarettes through a series of key presses (self-administration of cigarettes). Results showed that all three groups who received the phenylalanine and tyrosine deplete drink performed significantly ($p < 0.05$) fewer key presses to earn cigarettes than those who received the placebo drink. However, significant effects on craving were not observed.⁶⁶ Taken together, this suggests that depletion of phenylalanine and tyrosine may reduce motivation for nicotine seeking.

Polyunsaturated fatty acids

One preclinical and two clinical studies involving polyunsaturated fatty acids as treatment for alcohol dependence identified in this review.^{12,67,68} Two of the studies observed improvements in withdrawal symptoms.^{12,67} The third study did not.⁶⁸ In a study by Shi et al.¹², adult male mice were split into three groups. The fish oil group (FO+) received 50 μ L of FO (5 mg EPA, 30 mg DHA) for 14 days before alcohol treatment. The control group (CO+) and alcohol-free control group (CO-) received isocaloric corn oil daily. Fourteen days after administration of the fish oil, the FO+ and CO+ mice were

provided a liquid diet, which consisted of low-fat cow's milk, vitamin A, sucrose, and alcohol. The alcohol concentration in the liquid diet increased from 2% (v/v) on days 1-4 to 4% on days 5-14 and 8% on days 15-28. The alcohol-free CO- group was fed the liquid diet without alcohol. After the initial 28-days, the FO + and CO + groups were subjected to a 7-day abstinence period. Convulsive activity was examined using Handling Induced Convulsion (HIC) to measure physical distress. Results showed that treatment with FO+, compared to the CO+ group, significantly reduced ($p = 0.001$) convulsive activity in the acute withdrawal period at 6, 12, and 24 hours. In addition, after locomotor sensitization and CPP testing, mice treated with fish oil (FO+) and given alcohol for five consecutive days had a lower psychomotor stimulant response ($p = 0.03$). FO+ mice also showed a significantly decreased preference for an alcohol associated environment upon repeated ethanol exposure ($p = 0.023$) in CPP. This study suggests that supplementation with fish oil may attenuate some withdrawal symptoms and alcohol induced CPP.

Barbadoro et al.⁶⁷ conducted a randomized, double-blind, placebo-controlled study on patients at a facility for alcoholism treatment and rehabilitation. A total of 21 participants were split between either the intervention ($n=21$) or placebo ($n=10$). Participants were abstinent at the beginning of the 4-week program. Participants in the intervention group were provided with 1 g of fish oil per day (252 mg DHA and 60 mg EPA per 1,000 mg oil) for three weeks. Participants in the control group were provided 1 capsule of microcrystalline cellulose powder per day. ANOVA tests on the Perceived Stress Scale (PSS) scores between baseline and day 21 showed a significant ($p < 0.05$) decrease in perceived stress for the intervention group over the course of the study. Cortisol concentrations were also significantly reduced throughout the day in the

intervention group between T0 and T21 ($p < 0.05$). This clinical trial provides evidence exhibiting anti-stress effects with supplementation of fish oil, which may be beneficial during SUD recovery.

Lastly, research by Fogaca et al.,⁶⁸ consisted of alcohol dependent male subjects ($n=43$) that were thirty to fifty years of age. Participants were randomly placed into one of four groups: placebo; Naltrexone; PUFAS; and Naltrexone + PUFAS. Alcohol dependence severity (Short Alcohol Dependence Data, SADD) and craving (Obsessive Compulsive Drinking Scale, OCDS) was assessed at baseline and at the end of 90 days. All groups reduced the number of drinking days and improved SADD and OCDS scores. However, there was no statistically significant difference in drinking days and SADD ($p = 0.50$) and OCDS ($p = 0.69$) scores between the groups at the end of the three months. In this trial, supplementation with PUFAS, with or without naltrexone, did not result in reduced cravings or dependence.

Carbohydrate

In an animal model of relapse, Liu and Grigson⁶⁹ gave rats 14 days of cocaine (0.2 ml, intravenous injection) self-administration training followed by 90 days abstinence. In this trial, the rats learned that licking an empty spout 10 times resulted in an intravenous delivery of cocaine. The rats were then grouped by high or low spout licking responses into a 3% glucose + 0.125% saccharin solution group ($n = 8$) and a water group ($n = 8$). After 5 min access to glucose + saccharin or water, rats had access to the same apparatus previously used for self-administration, but no drug was given. The glucose + saccharin group made significantly fewer drug seeking attempts over the first 4 of 10 extinction trials. Once seeking behavior had been extinguished, rats were given a

priming injection of cocaine in a drug-induced reinstatement test. The water group relapsed to drug seeking while the glucose + saccharin group did not ($p < 0.005$). The results suggest that introducing a different rewarding substance may be beneficial to reduce use of addictive substances.

Clinical trials assessing the impact of dietary carbohydrates on addiction have shown mixed results. Helmers and Young⁷⁰ observed a significant ($p < 0.05$) reduction in withdrawal symptoms but not craving in 67 female smokers given a 50g sucrose drink compared to an aspartame placebo in a single test after 12 hours of abstinence. McRobbie and Hajek⁷¹ found no significant difference in a test of 44 men and women on nicotine replacement when given 12mg of dextrose, but a mild reduction in withdrawal symptoms in another 31 men and women using bupropion who were abstinent one week when compared to the placebo group. In a mixed cigarette cessation trial⁷² of 308 men and women using 3g dextrose tablets ad lib for four weeks, a nicotine patch, or both found a significant ($p < 0.01$) reduction in craving at one week in users of dextrose, but no differences in abstinence at trial end after four weeks. In another test assessing the effects of dextrose supplementation and smoking cessation, West et. al⁷³ gave 3g tablets of dextrose or sorbitol placebo to 16 male and female cigarette smokers who were abstinent one week and using nicotine replacement gum. After seven days, there was a significant ($p < 0.025$) reduction in craving score between the dextrose group compared to placebo group. Conversely, in a larger trial⁷⁴ ($n = 928$) using the 3g dextrose tablets for smoking cessation, West and colleagues found no significant difference in abstinence rates between intervention and control groups ($p > 0.05$). However, a possible limitation was that a different formula of dextrose tablets was used in this trial compared to a previous

trial. Taken together, using dextrose as a nicotine alternative may be effective but more research is needed to support this intervention.

Biery et al.⁷⁵ conducted a pilot study to assess the effect of a healthy diet (rich in complex carbohydrates, low in sugar, and caffeine free) on self-reported alcohol craving in patients (n=38) in a rehabilitation center. Eighteen patients followed a standard Alcoholics Anonymous rehabilitation program and 20 received nutrition counseling and diet therapy in addition to the standard rehabilitation program. For adults, the intervention lasted three weeks and for teenagers, 5 weeks. Patients who received the additional nutrition counseling and diet therapy reported a significant decline in alcohol craving scores upon completion of trial participation ($p < 0.02$). Biery et al.'s study suggests that eating a healthy diet may be beneficial in reducing alcohol craving.

Minerals

In a double-blind clinical study⁷⁶ regarding opioid dependence, 18 methadone-maintained males and females were given either magnesium in the form of an enteric-coated pill or placebo pill (n = 9/group). The magnesium supplementation was gradually increased over the 12 weeks. In week one, the intervention group received 366 mg/day of magnesium and in week 2, they received 549 mg/day of magnesium. In weeks 3-12, the participants received 732 mg/day of magnesium. The results revealed significantly fewer relapses in the magnesium group than in the placebo group after 12 weeks ($p = 0.04$). In summary, magnesium may be beneficial to use in tandem with methadone to reduce relapse in opioid dependence.

Ascorbic Acid

Levin et al.⁷⁷ created a device to mimic sensory factors of cigarette smoking by implementing an ascorbic acid (up to 300mg/day) dispenser in a cigarette shaped aerosol dispenser. Non-abstinent participants (n= 63) were randomly assigned to the cigarette substitute + counseling group or counseling only group. Each group received four group counseling sessions over three weeks. At the first and second counseling session, participants were instructed to switch cigarette brands, resulting in a 40% decrease in nicotine content each time. Participants were instructed to quit smoking at the third session and were provided with the aerosol device as a substitute. Subjects returned for a fourth counseling session two days after smoking cessation and a final session after another week. At the last two sessions, participants received information on methods to control cravings. At all meetings, carbon monoxide exhalation values were measured as evidence of smoking cessation and withdrawal scores (Shiffman-Jarvik⁷⁸) were documented. At the end of the study, the group using the aerosol device had significantly higher abstinence rates when compared to the counseling only group ($p < 0.05$). The reduction of nicotine relapse in this study suggests that providing a similar smoking alternative with ascorbic acid may reduce cigarette smoking. In a randomized, controlled trial, replacement of cigarettes with fresh lime was assessed by Rungruanghiranya et al.⁷⁹ Smokers who desired to quit were randomly assigned to two groups; (1) fresh lime (n= 47) or (2) nicotine gum (n= 53). The fresh lime group was instructed to suck on small pieces of lime and chew on the peel any time they had the urge to smoke. Follow up appointments were designated at 2, 4, 8, 12, and 24 weeks. Carbon monoxide exhalation measurements to confirm Continuous Abstinence Rate (CAR), self-reported craving and cigarette use, and behavioral counseling was conducted at each appointment. Results

showed CAR measurements did not differ in those using nicotine gum from weeks 9 through 12. The group provided with fresh lime showed a significantly ($p = 0.04$) lower rate of cigarette use than those using nicotine gum during week four only.⁷⁹ This study suggests that lime chewing may alleviate craving of nicotine and replace the need for nicotine replacement therapy.

Resveratrol

Resveratrol is a polyphenol found in several plant species, especially grape skins.⁸⁰ Red wine is the most notable resveratrol containing food item, containing an average of 1.4 to 12.3 $\mu\text{mol/L}$ of resveratrol.⁸¹ Hu et al.⁸² observed the effects of resveratrol in reducing cocaine-induced CPP and withdrawal related anxiety in rats. For the Day 1 and 2 CPP test, rats were allowed to explore three connected chambers to determine any preference. The time spent in each chamber was documented. Conditioned place preference training was induced from Day 2 through 7. Rats ($n=8$ per group) either received two injections of cocaine (10 mg/kg; C) or saline (S) 30 minutes apart in an injection-designated chamber. Rats were then moved and sequestered into an adjacent chamber for 30 minutes. After the CPP training, rats were allowed to freely explore the three chambers. Time spent in each chamber and the injection-designated chamber was recorded. Results showed that supplementation of resveratrol did not affect cocaine conditioned place preference during six days of cocaine exposure. In a separate group, 32 rats were assessed for cocaine abstinence-induced anxiety via elevated plus maze. On day one, rats were held in their home cages without intervention. Then, starting on day two, rats were injected with cocaine (10 mg/kg) for six days (day 2- 17) to create dependence. An abstinence period (day 8- 22) was combined with resveratrol (90 mg/kg) or saline (control) administration

on days 10-20. On day 23, rats were placed into the maze and documented for entries into open and closed arms, time spent in the open arms, and total distance traveled. Daily injections with resveratrol significantly ($p < 0.01$) increased rat entry and time spent in the open arms of the maze, suggesting resveratrol supplementation reduced anxiety behavior in rats during cocaine abstinence.

IV. DISCUSSION

This report aimed to compile evidence supporting nutrient or food component supplementation interventions to reduce craving, withdrawal symptoms, and relapse during substance use disorder recovery. Items of interest include N-acetylcysteine, polyunsaturated fatty acids, and magnesium. This review found that NAC reduced relapse to cocaine⁴⁷ and nicotine⁹ in rats, and reduced craving in cocaine-dependent participants.⁴⁷ NAC also increased cessation rates for nicotine⁴⁸ and cannabis users.⁴⁹ Mechanistic evidence provides insight to how NAC may reduce craving and relapse in SUD recovery. The metabotropic glutamate receptor mGlu2/3 is highly involved in regulation of glutamatergic cell signaling and abnormal signaling has been associated with drug craving.^{8,9} In rodents, NAC induces mGlu2/3 action which helps maintain extrasynaptic glutamate concentrations.⁹ Repeated exposure to cocaine, alcohol, and nicotine reduces glutamate/cystine (system Xc) exchange in glial cells of the nucleus accumbens, as well as reducing the concentration of basal glutamate.⁷⁻¹⁰ Supplementation of NAC has been shown to prevent the decrease in system Xc function during exposure to drugs, therefore maintaining glutamate/cystine homeostasis.⁷⁻¹⁰ Additionally, NAC provides cysteine for the production of reduced glutathione synthesis, assisting in maintenance of the reduced/oxidized glutathione ratio.¹⁰ Glutathione may be beneficial in reducing neuroinflammation and oxidative stress that occurs after drug use.^{83,84} Evidence supporting supplementation of NAC in SUD recovery is well-supported.

Mechanistic evidence also supports supplementation of other amino acids or amino acid intermediates such as L-theanine, kynurenic acid, serine, sarcosine, phenylalanine, glutamine, L-5-hydroxytryptophan, and tryptophan to support SUD

recovery. L-theanine supplementation reduced withdrawal symptoms in mice, and this result may be related to the known anti-anxiolytic effects of L-theanine.⁸⁵ Furthermore, L-theanine has been shown to increase alpha waves in the brain which are related to relaxation and increased focus, which could be related to better decision making, thus reducing risk of relapse.⁸⁶ Kynurenic acid, a metabolite of tryptophan, is found in brain tissue and is a non-selective excitatory amino acid antagonist.⁸⁷ During withdrawal, it has been shown that neurons in the locus coeruleus have an increase in activity.⁸⁷ As reviewed in the study from Rasmussen et al., direct injection of kynurenic acid into the locus coeruleus showed a significant decrease in withdrawal symptoms.⁸⁸ The results from Rasmussen et al. and other supporting evidence suggests that excitatory amino acid receptors in the locus coeruleus are a factor in drug withdrawal symptoms by observation of attenuation of withdrawal symptoms via kynurenic acid.^{88,89} D-cycloserine and D-serine are NMDA agonists at the glycine site of the NMDA receptor and in this review exhibited a reduction in cocaine-induced conditioned place preference in a murine model.⁵⁵ In addition, sarcosine reduces synaptic uptake of endogenous glycine by inhibition of the glycine transporter-1.⁹⁰ A plausible mechanism of action for these amino acids and amino acid intermediates relates to the NMDA receptor association with learning, memory, and synaptic plasticity. Previous evidence has suggested that D-cycloserine increases activity of NMDA receptors which may enhance association and extinction learning and memory.⁹¹ It can be speculated that these NMDA agonists and the inhibition of glycine transporter-1 increased the activity of NMDA receptors, therefore weakening the formation of cocaine-induced conditioned place preference.

During alcohol consumption, levels of endogenous opioids are increased.¹⁹ It can be inferred that this opioidergic decrease is a factor contributing to symptoms of alcohol withdrawal.⁹² To attenuate the breakdown of endogenous opioids, Jukic et al. supplemented D-phenylalanine, an enkephalinase inhibitor, in an attempt to reduce alcohol withdrawal symptoms.⁵⁹ In addition, precursors of the dopamine neurotransmitters, L-5-hydroxytryptophan, were supplemented in the attempt to maintain basal levels of dopamine in reward pathways during withdrawal.⁵⁹ Another approach of amino acid supplementation was suggested with the supplementation of tryptophan in addition to a high carbohydrate diet. Bowen et al. hypothesized that mood and serotonin levels may affect the level of withdrawal a person feels during nicotine cessation.⁶¹ High levels of tryptophan have been shown to out-compete other amino acids for entry across the blood brain barrier, therefore in theory providing additional substrate for the creation of serotonin. In addition, providing a high carbohydrate, low protein diet further removed tryptophan-competing amino acids from the diet.⁹³ Additional research is needed to assess how mood affects SUD, as well as the long term effects of tryptophan enrichment. Currently, evidence supporting supplementation of individual amino acids is limited.

Three tryptophan depletion studies were reviewed, all providing insignificant results for reducing craving or withdrawal symptoms during abstinence.²⁹⁻³¹ One trial assessing phenylalanine and tyrosine depletion showed evidence for reduced motivation for nicotine intake but showed no significant results for craving reduction.⁶⁶ During nicotine cessation, increased serotonin activity and serotonin receptor sensitivity has been associated with withdrawal symptoms.⁹⁶ In addition, it has been shown that nicotine use induces feelings of reward through dopamine release.⁹⁷ The theory of amino acid

depletion to reduce withdrawal symptoms is to reduce levels of serotonin and dopamine by restricting the intake of the neurotransmitter precursors tryptophan, and phenylalanine and tyrosine, respectively. However, the restriction of these amino acids may not reduce levels of serotonin and dopamine due to the stability of the amino acid pool in the human body. Amino acids compete for transport during absorption and to cross the blood brain barrier, therefore supplementation of a single amino acid can create imbalances over time. Additionally, the amino acid pool is tightly regulated and maintains a constant balance of amino acids, and therefore can be continuously drawn upon to provide the amino acids needed to create neurotransmitters. Furthermore, whether or not exogenous sources of protein or amino acids are consumed, the body can create or breakdown endogenous protein to provide tryptophan, phenylalanine, and tyrosine as needed.⁹⁸ At this time, evidence supporting amino acid depletion is limited.

Mechanistic evidence from animal models^{11–13,99–101} supports the positive outcomes of omega-3 fatty acid supplementation studies^{12,67,68} in this report by observing omega-3 fatty acid induced beneficial alterations in the brain of drug-dependent rodents. For example, previous evidence has shown rats deficient in omega-3 fatty acids have significant decreases in dopamine and the dopamine type-2 receptor (D2R) in the mesocortical system and an increase of these in the mesolimbic system when compared to non-deficient rodents.^{99–101} Omega-3 deficient rodents also have a significantly lower amount of vesicular storage pools of dopamine, possibly due to a decreased expression of vesicular monoamine transporter.^{99,100} Omega-3 supplementation has been shown to increase the expression of D2R in the nucleus accumbens, preventing the loss of D2R seen in morphine-dependent rodents.¹¹ The positive results seen in polyunsaturated fatty

acids studies may be due to the restoration of D2R levels in the nucleus accumbens and frontal cortex, thereby supporting normalized functioning of the reward pathway during periods of abstinence.

Additional effects of omega-3 supplementation were demonstrated in other reports found in this review. Chronic alcohol exposure in rodents caused increased expression of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA), resulting in abnormal medium-sized spiny neurons, abnormal synaptic clearance, and abnormal neuronal plasticity in the nucleus accumbens.^{12,13} Shi et al. demonstrated that supplementation with fish oil reduced the expression of AMPARs and protected neurons in the nucleus accumbens from alcohol-induced neuroadaptations in mice.¹² In addition, the same study observed a decline of PSD-95 (a membrane-associated signaling protein) expression in alcohol exposed mice with fish oil supplementation. Previously, PSD-95 has been shown to increase in alcohol-exposed rodents, resulting in abnormal scaffolding spaces and possible alteration of actin signaling cascades.¹⁰²

Clinical trials exploring the relationship of polyunsaturated fatty acids and drug abuse have shown an association of reduced plasma omega-3 levels and increased relapse susceptibility.^{103,104} Overall, there is evidence supporting the recommendation of the use of long-chain omega-3 fatty acid supplementation for nutritional support for SUD recovery.

There is limited evidence supporting the replacement of drugs of abuse with dextrose. Of the six trials reviewed⁶⁹⁻⁷⁴, three provided a significant reduction in withdrawal, craving, or relapse during abstinence. However, as nutrition professionals we

cannot advise increased intake of sugar at the levels used in reviewed studies, due to the increased risk of obesity, cardiovascular disease, and diabetes.¹⁰⁵ In contrast to giving carbohydrate in this alternative natural reward model, another study that did not fit the review criteria examined the absence of carbohydrate. Denker and Molander, et. al.¹⁰⁶ found that a ketogenic diet given to 58 rats significantly reduced alcohol withdrawal symptoms ($p < 0.05$). Evidence shows that chronic alcohol use shifts brain metabolism from glucose to acetate, a metabolite of alcohol. It has been hypothesized that a ketogenic diet can provide more energy to the brain with ketone bodies and decrease the use of acetate, therefore possibly improving brain function to relieve withdrawal symptoms.^{106–108} Considering the evidence against over-consumption of simple sugars¹⁰⁵, there is insufficient evidence at this time to support using carbohydrate for nicotine cessation. In addition, it may be counterproductive to trade nicotine dependence for high levels of glucose. While both nicotine and high levels of glucose are rewarding, both are detrimental to health. Further research on the ketogenic diet to support recovery should be explored due to current limited evidence.

Magnesium supplementation may induce anti-relapse effects as seen in the trial from Margolin et al.⁷⁶ Several mechanisms may explain how magnesium elicits effects in opioid dependence. For example, it has been hypothesized that supplemented magnesium inhibits calcium dependent dopamine release in response to drug intake¹⁰⁹, possibly reducing feelings of reward during drug use. Additionally, Nechifor¹¹⁰ and Kimes et al.¹¹¹ suggest magnesium inhibits nitric oxide synthase, resulting in reduced generation of nitric oxide. Nitric oxide activity has been associated with opiate withdrawal symptoms, possibly due to an increase of reactive nitrogen species, and inhibition of nitric oxide

synthase has been shown to attenuate withdrawal symptoms in rats. At this time, the evidence for supplementation of magnesium to reduce relapse in MAT patients is promising.

Evidence for ascorbic acid in recovery has limited support, however, of the two trials reviewed, both provided significant results in reducing nicotine relapse. Reduction of nicotine use may be associated with the ability of vitamin C to competitively inhibit dopamine binding.¹¹² It could be speculated that the addition of vitamin C inhibits the reward effect induced by drug use. Currently there is limited evidence supporting the use of vitamin C for substance dependence.

One study was reviewed assessing the effects of resveratrol on CPP in cocaine dependent rats.⁸² While supplementation with resveratrol did not change CPP behaviors, it did result in a significant decrease in anxiety-like behaviors. There is also supporting evidence for resveratrol in reducing symptoms of anxiety and reducing inflammation and oxidative damage.^{113,114} However, at this time, given the dearth of studies, evidence to support reduction of craving or relapse is limited.

Interestingly, this search did not identify several dietary components that may have potential to support individuals in SUD recovery. Evidence exists that calcium and vitamin D may assist in regaining homeostasis of the reward pathway, as well as reduce drug craving or seeking. In a pre-clinical study, supplementation of 1,25-Dihydroxyvitamin D3 in rats increased the mRNA expression of glial cell line-derived neurotrophic factor (GDNF).¹¹⁵ GDNF is neuroprotective to and assists in regeneration of dopamine neurons when exposed to dopaminergic toxins.¹¹⁶ Additional data from Trinko et al.¹¹⁷ provides supporting evidence for supplementation of vitamin D3. Administration

of calcitriol upregulated transcription of the *Th* gene, which produces the enzyme tyrosine hydroxylase for dopamine synthesis, and the *Slc6a3* dopamine transporter gene.¹¹⁷ Furthermore, vitamin D receptors (VDR) have been found in dopamine producing neurons in the substantia nigra and ventral tegmental area, as well as in D1R and D2R containing neurons in the nucleus accumbens and dorsal striatum. In mouse models, supplementation of calcitriol only upregulated the expression of D2R in the nucleus accumbens.¹¹⁷ In rat models from Trinko et al., subjects administered with calcitriol displayed a significant increase in dopamine release when exposed to amphetamine, in comparison to controls. In mice models, calcitriol administration significantly reduced self-administration of amphetamine.¹¹⁷ Further, a clinical study observed the association between calcium, vitamin D, and alcoholism in alcohol-dependent subjects (n=47). Results revealed higher breath alcohol was associated with lower plasma calcium levels, decreased calcitonin levels were found in high risk alcoholics, and decreased vitamin D concentrations were seen in all participants.¹¹⁸

Additionally, calcium could be beneficial for recovery through regulating dopamine release via voltage-sensitive calcium channels. Recent studies revealed the medication used to assist in alcohol cessation, acamprosate, may provide a strong interaction with alcohol via its calcium component.^{119,120} A supporting preclinical trial from Sanghvi and Gershon¹²¹ observed a significant reduction in naloxone induced withdrawal symptoms in morphine dependent male Sprague Dawley rats (n = 8/group) given ad lib access to calcium in water (97mg/100ml) and pretreated with 45mg/kg intraperitoneal injection, when compared to the control group. There is limited evidence supporting calcium supplementation to reduce withdrawal symptoms.

Strengths of this systematic review include that it encompasses both animal and human trials that assess nutrient or food component supplementation in substance use disorder recovery. In addition, the human trials included in this review are comprised of male and female subjects, as well as individuals with different ethnic backgrounds, providing a subject pool representative of the general population. To our knowledge this is the first review that has assembled the research on the topic of food component interventions for supporting continued abstinence during recovery. Also, given that the length of time of nutrient or food component supplementation varied across trials, we were able to observe how trial length might influence significant change. Additionally, trials assessing nutrient intervention during methamphetamine abstinence were not found during the article search. Another weakness is the use of MAT and other substances such as alcohol, cannabis, and nicotine during some of the trials. While methadone, cannabis, alcohol, and nicotine may alter the results of nutrient or food component supplementation, we believe that assessing the effects of medical nutrition therapy in conjunction with these substances to be a more rational approach as these substances are often continued during the transition from abuse to cessation to recovery.

V. CONCLUSION

Nutrient or food component supplementation to treat SUD shows promise through this supporting body of evidence. Alterations in brain function associated with drug dependence coincide with several different processes such as glial cell glutamate-cysteine exchange^{18,47-49}, regulation of transcriptional and translational gene expression^{11,12,100,101,115,117}, and regulation of dopamine release.^{99,100,112} Craving and withdrawal relief may be induced with supplementation of food components by supporting and repairing reward pathways in the brain. Future research can focus on additional clinical trials assessing the efficacy of each nutrient or food component, as well as a multi-nutrient supplement, to reduce craving and relapse during SUD recovery.

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Declaration of interest. The authors have no relevant interests to declare.

Appendix S1 PRISMA checklist

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