A Biopsychosocial Overview of the Opioid Crisis: Considering Nutrition and Gastrointestinal Health

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The opioid crisis has reached epidemic proportions in the United States with rising overdose death rates. Identifying the underlying factors that contribute to addiction vulnerability may lead to more effective prevention strategies. Supply side environmental factors are a major contributing component. Psychosocial factors such as stress, trauma, and adverse childhood experiences have been linked to emotional pain leading to self-medication. Genetic and epigenetic factors associated with brain reward pathways and impulsivity are known predictors of addiction vulnerability. This review attempts to present a biopsychosocial approach that connects various social and biological theories related to the addiction crisis. The emerging role of nutrition therapy with an emphasis on gastrointestinal health in the treatment of opioid use disorder is presented. The biopsychosocial model integrates concepts from several disciplines, emphasizing multicausality rather than a reductionist approach. Potential solutions at multiple levels are presented, considering individual as well as population health. This single cohesive framework is based on the interdependency of the entire system, identifying risk and protective factors that may influence substance-seeking behavior. Nutrition should be included as one facet of a multidisciplinary approach toward improved recovery outcomes. Cross-disciplinary collaborative efforts, new ideas, and fiscal resources will be critical to address the epidemic.

Keywords: biopsychosocial (BPS) model multidisciplinary, opioid, nutrition, gastrointestinal, trauma, addiction, substance use disorder, microbiome

INTRODUCTION

The opioid crisis in the US has received extensive coverage in the media leading to increased awareness of this “public health emergency.” Between 2000 and 2014, nearly a half million people in the US died from a drug overdose (1). Opioids accounted for 61% of all drug-related overdoses in 2014 (1). Overdose death rates are highest when opioids and benzodiazepines are combined (2). It has become increasingly clear that over-prescription of these medications in the past two decades is a primary upstream driver of the crisis. The rapid rise in costs associated with addiction treatment threatens the infrastructure and finances of many US hospitals (3). According to some estimates, the number of people currently dependent on opioids or heroin is more than three times greater than the current capacity to deliver treatment (4). The President’s Fiscal Year 2017 budget proposed allocating a billion dollars in an effort to reduce prescription drug misuse through the twenty-first Century Cures Act. However, despite increased resource allocation, policy changes, and changing cultural norms about addiction, little measurable progress has been made in reducing the problem. Relapse rates continue to be above 50% at 6 months (5, 6) and similarly high worldwide (7, 8).
Given the current crisis and the alarming rates of overdose and death associated with prescription opioids, illicit synthetic versions (i.e., carfentanil), and street heroin (1, 9), researchers have focused on identifying factors that contribute to addiction vulnerability (10). Numerous authors have hypothesized that there is an interaction between genetic factors (innate predisposition) and environmental and personal factors (collectively referred to as psychosocial factors herein). Furthermore, efforts to effectively reduce the opioid epidemic will require understanding individual differences that contribute to drug use initiation, as well as long-term neurobiological adaptations stemming from prolonged intake. Knowledge of these interactions may lead to improved treatment protocols that account for underlying vulnerability. Because the opioid problem is heterogenous, a wide range of treatments will be needed to target various geographical regions, age groups, and addiction severity. This review attempts to explore the interplay between social and biological factors, including potential mediators related to opioid use. A strong case will be made to consider nutrition in the treatment of opioid use disorder (OUD), whereas the role of opioid maintenance therapies is emphasized less due to extensive coverage elsewhere (11, 12).

### Pain Management

In 2001 The Joint Commission identified self-reported pain as a fifth “vital sign” for healthcare providers to consider, which led to the liberal use of pain-relieving medications. It has been suggested that the opioid crisis may be seen as a dual epidemic: one of abuse, and the other as the right to control poorly defined pain (13). While the concept of “self-reported pain” has generated considerable debate, the increasingly negative consequences associated with analgesics (pain killers) have necessitated intervention at multiple levels including hospital emergency departments where misuse and diversion are common (14). There is an urgent need for health care professionals to educate and realign patient expectations regarding pain management (15). By far the most common acute and chronic pain medications are opioid analgesics which include codeine, hydrocodone, oxycodone, morphine, and fentanyl, and others. In a study using data from 2000 to 2005, over half of patients taking prescription opioids beyond 12 continuous weeks were still using them after 5 years (16) underscoring the addictive potential of these drugs. Between 2002 and 2014 the odds of young adults (ages 18–34 years) having a prescription OUD doubled (17). In response to escalating abuse, makers of OxyContin released an “abuse-deterrent formula” in 2010 at which time heroin use began to rise (18). Between 2010 and 2014 heroin-related deaths tripled in the US (1).

### Medication Assisted Treatment

The Comprehensive Addiction and Recovery Act (CARA) signed by President Obama in July 2016 expanded funding for the availability of medication assisted treatment (MAT) for OUD. MAT consists of pharmacotherapy, ideally in conjunction with behavioral health intervention. Medications such as methadone and buprenorphine (Subutex) have proven effective in mitigating the negative side effects associated with OUD (19). More recently Suboxone (buprenorphine plus naloxone) has replaced Subutex due to its lower abuse potential. Naloxone (Narcan) can reverse the effect of overdose and is recognized by CARA as a primary agent for saving lives. Naloxone is a competitive inhibitor of brain opioid receptors, while naltrexone is a similar blocking agent used for relapse prevention by impeding the euphoric effect of opioids, as well as the rewarding effects of alcohol. The use of MAT has grown in recent years and is now considered the most common practice for treating OUD. MAT can be considered a “harm reduction” or “risk mitigation” strategy compared to traditional models of addiction treatment which have focused on complete abstinence after the detoxification period. Ideally, the goal of MAT is to move patients toward abstinence, but many stay on MAT for extended periods of time.

### Theoretical Framework

The biopsychosocial (BPS) framework was originally proposed in 1980 by Dr. George Engel stemming from his dissatisfaction with the biomedical model of illness (20). BPS draws its conceptual roots from the general systems theory which originated in the 1950s and aimed to unify knowledge and theories across different disciplines into a systemic vision of a “better world” (21). The BPS model has been promoted by the field of psychosomatic medicine utilizing “mind-body” approaches to health (22) that are common in “alternative therapies” (e.g., meditation, acupuncture, nutrition). A central theme with this approach is the use of seemingly divergent conceptual models to emphasize multicausality in understanding disease, rather than a reductionist approach. An example of a similar approach known as Ecosocial Theory was introduced by Krieger (23). The interactive BPS model proposes an integrated vision of health and disease that does not focus on a single root cause which is seen in a traditional biomedical approach (24). The integration of social and biological processes (25) may be critical for OUD treatment since the reductionist biological model has not been productive (and arguably harmful) and capitalized on by the pharmaceutical industry (26). A BPS framework not only helps guide addiction treatment, but also influences public perception of addiction (27).

This comprehensive review examines the opioid crisis using a biopsychosocial framework (see Figure 1) with particular emphasis on (1) social and environmental factors (2) psychosocial factors (stress, trauma/adversity) and (3) biological factors (including potential mediating mechanisms). In analyzing the opioid crisis at the individual as well as population level, a case will be made for considering alternative treatment modalities for OUD such as the emerging role of nutrition, with emphasis on gastrointestinal (GI) health.

### SOCIAL AND ENVIRONMENTAL FACTORS

#### Environmental Factors

Many researchers and health care professionals believe that the opioid epidemic is mostly a consequence of “supply side” abundance, resulting from aggressive marketing by the pharmaceutical industry as well as physicians who have over-prescribed. A recent public opinion poll identified physicians as being responsible for the crisis (28). Given the link between
prescription opioid use and later onset of heroin abuse, an obvious public health strategy is to focus on reducing improper opioid prescriptions. The Center for Disease Control (CDC) has recently issued guidelines stating that non-opioid therapy is preferred for chronic pain outside of active cancer, palliative, and end-of-life care (29). Other authors believe that restricting the ability of physicians to write prescriptions is only a short-term fix (30). New Cures Act requirements for prescribers are currently underway.

Supply-reduction efforts have had some success (18). However, evidence suggests that those already dependent on prescription opioids frequently transition to heroin when their supplies are cut off (31). Data from 2015 shows that a third of people in treatment for OUD began with common prescribed opioids and progressed to heroin use (31). Other research has shown that as many as 80% of heroin users started with prescription opioids (32). There is a genuine concern that individuals who originally benefited from opioid medications will turn to purchasing drugs from an illicit market if their prescriptions are stopped (33). Recent data shows alarming rates of chronic pain preceding the onset of OUD, associated with high rates of mental disorders (81.7%), suggesting a high risk of transitioning to illicit drugs if stopped abruptly (34).

Can the issue of opioid misuse be tackled on the supply side alone? History suggests not. Legislative efforts at the State level to close “pill mills” have had little discernable impact in reducing opioid use (35). Other recommendations to tighten control include protocols to ensure authenticity of the prescription source, adding additional abuse detection steps, and practices for returning unused drugs (36), as well as more physician education during residency training (37). While it is hopeful that policy interventions can reduce overdose and death, solutions to control illegal heroin coming into the country are less obvious and fall under the jurisdiction of the Drug Enforcement Agency (DEA). Heroin arrests have been increasing in some states (38). Interventions focusing only on prescription opioids are unlikely to be sufficient as long as heroin and other synthetic opioids such as fentanyl and carfentanil continue to flood the market. Illicit drugs are increasingly available through the “dark web” and

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**FIGURE 1 | A biopsychosocial perspective on substance consumption.**

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ACEs: Adverse Childhood Experiences
are an important but less documented mechanism driving the opioid crisis. The environment in which one resides is a known predictor of consumption behavior (39), thus behavioral economics is a conceptual system to understand how one's access and exposure will predict demand and subsequent intake (40–43). Historically, research on human choice has been dominated by economic theory. Eventually it became clear that the quest to “maximize utility” could not capture human preference (44) nor would it apply to disorders such as addiction. Behavioral economics is a scientific discipline at the intersection of economics and psychology as it pertains to health-related behavior (45). It has been used to study decision making in the context of substance use disorders (SUD) (46–48) including alcohol (49) and other health behaviors such as food and drink consumption (40, 50). This construct may be useful to make connections between the environment and consumption behavior (Figure 1).

**Socioeconomic Status (SES)**

The relationship between opioid prescribing practices and SES has not been extensively studied. US data from 2006 to 2009 suggests that patients presenting to emergency departments from lower SES regions were less likely to receive opioids for equivalent levels of pain compared to those from more affluent neighborhoods (39). In a more recent study of the association between new back pain diagnosis and opioid medication use, low neighborhood SES has been linked to significantly higher opioid prescription rates, suggesting the possibility of higher inappropriate narcotic use (poor physician guideline compliance) in less advantaged areas (51). Meanwhile, heroin use has significantly increased across most demographic groups (41). In an ecological study of one Southern California county from 2010 to 2014 (n = 1,205) higher education and income were protective against opioid-related deaths but the data suggests that no group is immune and there is dire need for public health interventions at all SES levels (42).

Norwegian data suggests that individuals with a drug-related death had lower SES than the general population but overall SES situation prior to death was heterogenous (41). A large dataset from Kaiser Permanente Northern California showed that prescription opioid use is lowest in the most deprived neighborhoods (52). Conversely, other Kaiser reports using a larger dataset have found individuals living in deprived neighborhoods are more likely to become long-term users (53). The CDC has examined county-level factors associated with prescribing patterns and have found higher opioid use in regions with higher rates of unemployment and Medicaid enrollment (54). Pregnant women using opioids as their primary substance have the highest prevalence in the Southern US and are less educated (43). Other research on pregnant women in the US have shown similar education gradients and higher opioid use below $20,000 annual household income (55) which is consistent with national data linking lower levels of income to opioid misuse (56).

In a rural part of Wisconsin (92.6% White, median income $46,333), a majority of overdose patients had private insurance (57) which is contrary to national data suggesting higher rates of overdose among the uninsured (41). Given that SES is an important predictor of health care utilization, more research is needed on OUD in uninsured populations in order to truly capture the effect of SES on opioid prevalence rates and health outcomes. Recent data suggests opioid use plays a critical role in fueling rising suicide rates (58). Inconsistent findings between SES and opioid misuse and death necessitates longitudinal data in order to track changes in these relationships over time.

Despite these inconsistencies in the opioid literature, in public health SES should always be considered when examining health outcomes and building interventions. The BPS Perspective considers how socioeconomic disadvantage can be deleterious (Figure 1, path B), or how socioeconomic advantage can be protective against negative outcomes associated with drug use (via environments that support wellness). Figure 1 includes a pathway where substance consumption stimulates “reward” (discussed in section Reward Pathways) leading to “well-being” (path 1) which does not feedback to negative affect and craving. The model considers multiple substances (including food, beverages, and caffeine) which are generally less subtle (less dopaminergic) in their addictive potential when compared to drugs, alcohol, and nicotine. Thus, the framework is designed to conceptualize negative health outcomes but is flexible regarding psychosocial protective factors, therefore comprehensive and not limited to OUD.

**PSYCHOSOCIAL FACTORS**

**Trauma and Stress**

Efforts to reduce supply alone are unlikely to resolve the opioid abuse problem in the US. It is possible that some of the pain associated with opioid dependence is psychological. In other words, opioid misuse may be a coping mechanism for unresolved emotional pain that cannot be easily addressed in other ways. Allostasis describes the body's adaptations to predictable or unpredictable changes in the environment. McEwen's concept of allostatic load (59) is an early example of how social and biological factors integrate to influence health outcomes. More recently Koob fit an allostatic model to addiction where the brain is challenged to self-regulate under stress, and subsequent changes in corticotropin-releasing factor (CRF) further compromise neurocircuitry (42).

Post-traumatic stress disorder (PTSD) causes changes in fear and stress-related biology including hyperarousal, trauma cue-dependent recall, avoidance, and extinction memory deficits, among others (60). According to one study, numbness or detachment as a result of trauma exposure appears to be the PTSD symptom most strongly associated with pain-related outcomes (61). Co-occurring PTSD and SUD has also been associated with insomnia (62) which can negatively affect health. A recent study on veterans demonstrated that buprenorphine use was associated with a significant improvement in PTSD symptoms after 8 months (63) highlighting overlapping mechanisms between SUD and PTSD.

Neuroimaging studies have shown that trauma has a measurable, enduring effect on the functional dynamics of the brain, even in the absence of clinically diagnosable PTSD (64). In a large national sample, the presence of PTSD increased the
risk of developing OUD after exposure to opioid painkillers (65). These findings suggest that neurobiological imprints of PTSD such as the release of CRF during periods of activation/arousal increase susceptibility to addiction. Recent evidence suggests that the association between PTSD and opioid use is more pronounced in women than men (66). A recent case study described a woman who was diagnosed with major depressive disorder and OUD, but later was identified as using opioids to self-medicate her underlying undiagnosed PTSD (67).

Deficits in reward functioning may be a mechanism underlying anhedonia (lack of pleasure) associated with PTSD (68). The trauma theory suggests that opioids are distinctly reinforcing to individuals with PTSD (69). While this explanation will not occur in all cases of OUD, it may represent a distinct subtype. It appears likely that physical changes associated with trauma create increased risk for SUD, lending support to the BPS Perspective (path E). Better detection and integrated treatment for comorbid PTSD and OUD may be helpful. Several authors have suggested that PTSD screening should be routine for clinicians who prescribe opioids (65), particularly for chronic pain syndromes (61).

**Adverse Childhood Experiences**

A considerable amount of research has connected adverse childhood experiences (ACEs) to a dose-dependent increase in risk for drug abuse (70, 71). Strong links between ACEs and the initiation of opioid use have been described (72, 73). ACEs have been linked to age of opioid initiation, intravenous use of the drug, and lifetime overdose in a graded, dose-response manner (73). Potential mechanisms mediating this relationship could be environmental (e.g., poverty, parental criminal justice involvement) as well as biological (e.g., genetic heritability, altered neurodevelopment). Given the significant associations with childhood abuse and prescription opioid use, several authors have identified child maltreatment as an important social and environmental factor (path B) which should be considered in prevention and intervention efforts amidst the crisis (74, 75).

Some authors have suggested that resources should be invested into policies and programs that prevent ACEs as a mechanism to reduce substance misuse (76). Overall, the findings underscore the importance of OUD treatment being guided by trauma-informed modalities, including “complex trauma” (different from PTSD) (77).

**Psychosocial Vulnerability**

The “brain disease model of addiction” has been challenged by some authors who advocate for an addiction disease model that includes the presence of a pre-existing disorders such as anxiety or depression (78). Rodent studies have demonstrated that social isolation leads to an increase in drug self-administration (79). Sociological research has identified that neighborhoods with high crime and deviance rates are associated with higher rates of opioid misuse among adolescents ages 12–17 living in socially disorganized areas (80). Substandard environmental factors related to SES and structural racism can “get under the skin” and create health problems including addiction (81). The social determinants of health are thus an important part of the overall BPS Perspective on opioids, linking the Life Course Perspective (see section Life Course Perspective) to SES and environment.

The PTSD susceptibility model suggests that OUD can lead to increased psychosocial vulnerability via negative experiences associated with drug using (procurement, intoxication, increased risk of accidents, and violence) (69). However, the more common theory is the “self-medication hypothesis” (69, 82) which suggests individuals turn to opioids to reduce stress, pain, and unresolved psychological trauma (path C–F). This hypothesis has also been described as “latent vulnerability,” suggesting that childhood neglect increases the lifetime risk of developing a psychiatric disorder (83). One proposed mechanism of vulnerability to addiction includes a compromised ability to regulate emotions effectively (84). Other research has identified increased impulsivity as a significant moderator between PTSD and substance misuse (85, 86) as well as the role of negative urgency within this relationship (87). More research is needed on the direct link between stress and dopaminergic reward pathways associated with OUD.

**BIOLOGICAL FACTORS**

**Reward Pathways**

Consumption of substances activate mesolimbic reward pathways (path H). Despite some disagreement (88), most authors understand SUD to be a brain disease associated with weakened executive functioning leading to poor self-regulation and repeated relapse (89, 90). Neuroimaging studies have revealed biomarkers in the corticolimbic (91) and corticostratial regions that may be predictors of relapse (92) in the face of drug cues (93). Altered neurotransmission in frontostratial circuits have linked multiple forms of impulsivity to drug-seeking behaviors (94). A specific understanding of the reward process related to the opioid epidemic necessitates an understanding of pain pathways viewed as anti-reward processes associated with dopamine (DA) deficits (95). A recent review describes how inflammatory processes may decrease DA synthesis and availability via multiple pathways (96).

Animals models have demonstrated impaired incentive learning in early opioid withdrawal resulting in maladaptive reward seeking (97) which in some cases can last a lifetime (78). The persistence of a learned association with pain relief provides the continued motivation for seeking opioids, particularly in the face of distress or dysphoria (path E). These learned associations of relief from an aversive mental state, either pre-existing or created by the withdrawal drives the craving cascade in susceptible individuals (78). It is likely that repeated use perpetuates anhedonia, and thus interferes with chances of long-term recovery (98). Negative affective states during the period after substance consumption are an important part of the withdrawal-craving cascade (path J). It has been shown that in the absence of the substance, negative moods (e.g., depression, anxiety) coupled with enhanced sensitivity to stress eventually create obsession-like preoccupation (brain becomes “hi-jacked”), a loss of executive functioning, and then relapse, reinitiating the cycle again (89). In Figure 1 the preoccupation-craving feedback
Neuroeconomics

Neuroeconomics is behavioral economics plus neuroscience (108) and has been referred to as "decision neuroscience" (109). Techniques such as functional magnetic resonance imaging (fMRI) have introduced biophysical data into behavioral economics in order to understand how value maximization is computed at the neural level. These include choice anomalies (44), deviation from rationality (49), and delay discounting (preferences for smaller immediate rewards relative to larger delayed rewards) (49, 110). This emerging field is highly relevant to our current understanding of SUD as a neurobiological disorder which impairs information processing (111). Several circuits responsible for processing input can lead to craving and relapse, including disorders of storage (learning and memory) and disorders of access (to decision making processes) (111). Executive dysfunction has also been associated with stress and has been linked to the SES gradient, as well as negative health behaviors (112). Neurobiology should play a more central role in our theoretical understanding of valuation (110) and choice (44). Efforts to understand circuit-specific variation in different individuals has the potential to tailor disease-augmenting therapies. Neuroeconomics can be viewed as a mediator between reward pathways and consumption behavior in Figure 1, with more details reviewed elsewhere (108, 113).

BIOLOGICAL MEDIATORS

Interest in the biological imprint of trauma has been growing. The biological correlates of complex trauma have been described across various brain regions (e.g., hippocampus, amygdala), throughout the autonomic nervous system (e.g., vagus nerve), in various neurobiochemical measures (e.g., cortisol), and across genetic as well as epigenetic factors (41) (path C). Environmental stress has the potential to alter lifelong hypothalamic-pituitary-adrenal (HPA) axis function and to induce subsequent neurodevelopmental maladaptation (51) (path A). The HPA axis is important for the production of glucocorticoids (e.g., cortisol) in response to physical and mental stress. Research elucidating mechanisms which link social and environmental factors to individual physiology is still in its nascent stages.

Epigenetics

Epigenetics describes the interaction of genes with their environment. Maternal child health research has identified "critical periods" where epigenetic modifications are particularly impactful (51). This emerging field looks at changes that occur in the brain as a result of drug administration, with particular interest at mu-opioid receptor cites in the nucleus accumbens and ventral tegmental area (114, 115). Epigenetic changes during stressful social circumstances may predispose individuals to drug abuse (116) (path F). In utero stress exposure has been associated with DNA methylation changes leading to long term alterations in gene expression (117) which can alter the course of brain development (118) (path D). Prenatal exposure to maternal stress has been associated with a range of mental health disorders (119) including the development of eating disorders (120). Animal
models have demonstrated that addiction-like eating during gestation and lactation can program the offspring for addiction-like behaviors including drug-seeking (121, 122). The overlap between nutritional programming and altered incentive motivation via the mesolimbic dopaminergic system (123), it is being hypothesized that eating behaviors in recovery from OUD may impact reward pathways and be mediated by epigenetic and microbial mechanisms. Further study on the impact of nutrition on genetic expression of addiction traits are warranted.

**Microbiome**

Research on the gut microbiome has increased exponentially in the past decade. A state of equilibrium (i.e., homeostasis) serves health, whereas a compromised state (e.g., gut permeability) promotes dysbiosis, inflammation, and susceptibility to disease (124). Many authors have suggested that our gastrointestinal microbiome may be a key factor impacting our emotional and behavioral health (125). Changes in the composition of gut microbial profile (including byproducts from degradation of food) have been shown to modify regulation of genes (epigenetics) involved in depressive disorders (126). Systematic reviews have suggested positive effects of probiotics on depressive symptoms (127, 128). Diets rich in fiber and omega-3 have been shown to reduce the risk of depression, anxiety, and stress (129). Investigators have begun to consider potential connections between PTSD and the microbiome, mediated by the immune system and HPA axis (130) (path C). This area of investigation is an excellent example of how environmental, psychosocial, and biological factors clearly interact to influence health. The microbiome as a mediator has created a paradigm shift in neuroscience and psychiatry (131), highlighting the importance of nutrition that goes beyond the basics of macronutrients. A recent publication states: “attention to the microbiome may help answer nagging questions about the underlying biological mechanisms that link social conditions to health” (132). Some social scientists may view this as a reductionist approach, but it may prove to be the opposite.

The role of the gut-brain axis in determining food reward (133) has led to the possibility that microbes inside our intestinal tract may be influencing our consumption patterns (134, 135) (path G) through conditioned food preference via hormonal and dopaminergic mediators (133) (path F). It has been argued that bacterial species aim to increase their chance of survival (just like other organisms) and have a wide range of mechanisms to influence host consumption behavior, including production of neurotransmitters and short-chain fatty acids, manipulation of intestinal barrier function, and signaling along the vagus nerve (134, 136). This “puppeteer” theory has been challenged by the argument that microbial ecology has local effects on the gut stemming from an evolved dependence rather than direct human behavioral manipulation (137). Meanwhile, authors have speculated on the possibility that alterations in the gut ecosystem may be part of the etiology and progression of eating disorders (138).

The question is: how is the microbiome linked to AUD or SUD? This emerging topic considers neuroendocrine pathways that are involved in addiction, where gut microbiota may play a causal role (139). In regard to alcohol, several lines of evidence in both animals and humans have demonstrated a gut-liver axis which links inflammation, intestinal permeability, and immune function, to both liver and colon disease (140–143). More recently it has been proposed that dysbiosis associated with alcoholism induces neuro-inflammation via the central nervous system which can produce anxiety, depression, craving, as well as drinking behavior (144, 145). Links between the microbiome and OUD will be described in more detail below.

**OPIOIDS AND NUTRITION**

There is a paucity of high-quality evidence regarding the role of nutrition in OUD recovery. Nutrition does not easily lend itself to randomized controlled trials given the amount of time needed for measurable outcomes, and the presence of confounders introduced during this period. Therefore, nutrition research has been constrained to reductionistic approaches, such as looking at single nutrients or single outcome measures such as changes in weight. Conducting research on SUD populations creates additional challenges, as there are often high attrition rates (146). Biopsychosocial approaches to future nutrition research will hopefully renegotiate the boundaries between physical and mental health by targeting the gut-brain axis and examining novel outcomes.

**Eating Behavior**

A high preference for sugar and sweetened foods has been consistently described during early abstinence from opioids (147–149). Not surprisingly, available evidence suggests low fiber intakes (147, 150). During active heroin use, individuals report little interest in food, preferring quick and cheap convenience foods (151). During early abstinence there is evidence of binge eating and addiction-like eating behaviors (152) as well as concerns about weight gain (153). Individuals on methadone maintenance predictably gain weight (154) particularly among females (155), and this effect is higher for individuals with less knowledge about healthful eating (156). It is possible that altered hormones associated with heroin addiction contribute to abnormal weight changes (157) and/or decreased bone mass (158). Less is known about how eating behaviors during the early months/years of recovery impacts reward processing. Given that highly palatable food can be very rewarding, it is not surprising individuals in early sobriety seek out these foods (159). A study evaluating the impact of nutrition on the reward-related neurochemistry of OUD patients has not been done.

**Nutrient Deficiencies**

Vitamin and mineral deficiencies associated with opioid addiction have been well-described (160–165). However, given the retrospective nature of the research, it is difficult to determine if deficiencies are caused by poor dietary habits, by the drugs themselves, or possibly from impaired absorption. Opioid users can be considered at high nutritional risk (166) based on self-reported nutritional intake (167). Additionally, most of the opioid research has been conducted during methadone maintenance (162, 168–170), due to the difficulties
conducting research on individuals using illicit drugs. Some studies have shown elevated serum values of malondialdehyde (167), homocysteine (171), and leucocytes (171), all of which serve as markers of inflammation. To date, a study on the use of nutrition therapy to reduce inflammation in OUD subjects has not been conducted.

**Gastrointestinal Health**

OUD has been associated with bowel dysfunction including but not limited to constipation while using and diarrhea during detoxification (172). While laxatives and other over-the-counter remedies can be used to treat opioid-induced bowel dysfunction, they do not address underlying causes which may include microbial alterations (173). Several papers have addressed opioid-related GI concerns, yet no authors make any specific nutrition recommendations (174, 175). Given how challenging it is to conduct nutrition interventions in SUD detox settings, it is not surprising there is a lack of evidence. Meanwhile, clinical anecdote suggests that attention to a well-balanced diet during detoxification can minimize the intensity and duration of rebound diarrhea. Clinicians have been relying on case reports rather than published standards.

Activation of mu-opioid receptors in the gut wall inhibits pathways within the enteric nervous system, which in turn reduce motility, delay gastric emptying, and slow intestinal transit (172). Constipation typically persists as long as opiates are being administered, and emerging microbiome data presents compelling new questions related to the origins and consequences of pathophysiological motility. It has been shown that GI transit times are prolonged in the cecum and ascending colon, but not in the transverse or descending colon (175). Delayed gastric emptying (176) may create a motionless environment favorable to bacterial growth (177). It is possible that delayed GI transit time can increase intraluminal concentrations of toxins. Chronic opioid use in cirrhosis has been associated with increased endotoxemia, gut dysbiosis, inflammation, and all-cause hospital readmission (178).

Recent findings indicate that gut microbiota modulates physiological responses related to tolerance induced by chronic morphine administration (179). In a rodent model using morphine, a particular strain of bacteria (*E. faecalis*) increased 100-fold compared to placebo (180). These findings have been replicated, and it has been added that certain microbial communities associated with stress tolerance are reduced in the morphine-rodent model (181). Similar to alcohol, opioid ingestion can disrupt the intestinal epithelium (160) leading to bacterial translocation and subsequent inflammatory cascades (161). Animal models that have opioid-induced gut microbial disruption, altered cholesterol/bile acid metabolism and systemic inflammation can be “rescued” by microbiota fecal transplantation positively influencing gut health (162). It is not yet clear whether the microbiome can contribute to craving in OUD, or to what extent opioid-induced dysbiosis impacts mental status in humans. However, it has been shown that antibiotic-treated rodents transplanted with saline microbiota have restored reward functioning (163). Rodent models have also shown that gut microbiota plays a key role in pain (166).

Gut microbiome alterations and impulsive behaviors influenced by striatal dopamine receptor expression have reduced alcohol seeking in animal models (164). Meanwhile, interest in reducing neuroinflammation in opioid recovery is beginning to receive considerable attention (165). The gut-brain axis appears ripe for intervention strategies in OUD.

Given what is known about the links between gut and brain, it can be hypothesized that the microbiome is an important and modifiable mediator of substance-seeking behavior (paths F and G). It has been proposed that gut bacteria can influence neurobehavior including host appetite for food (135, 137, 182), so it is not implausible to predict associations between microbiota and all substances passing through the gut. A recent review summarizes bidirectional associations between drugs and bugs concludes: “it is not bizarre to think that in the future microbiome measures will form part of clinical practice to investigate either the efficacy or side effects of psychotropic compounds” (183).

**DISCUSSION**

**Theory Comparison**

Efforts to address the opioid epidemic are being led by pharmaceutical companies promoting new medications (MAT) as the solution. One major短coming is that it does not address individuals’ underlying psychological and emotional issues that contribute to addiction susceptibility. It examines the “macro” but not the “micro” environment, and one could argue that psychosocial factors require increased public health attention.

The psychosocial theory of addiction vulnerability is focused on the individual but is highly dependent upon social and environmental factors (path B). Disparities in population health are known to differ on the basis of social rather than biological factors (168). Individuals with a history of PTSD, complex trauma, stress, or ACEs can experience physiological as well as emotional changes that increase the likelihood of opioid addiction. The trauma theory of addiction suggests that opioids are strongly reinforcing to individuals with PTSD (69) and may initially treat the aversive symptoms. Improving social factors that decrease trauma, stress, and pain appear to be an important goal but are unlikely to be effective without reducing the overall supply and accessibility of opioids.

The biological theory of the opioid crisis may help inform future pharmacological interventions targeting key neurohormonal and/or microbial systems. An in-depth understanding of the neuroscience of addiction can also improve behavioral interventions targeting the cognitive aspects of relapse and recovery. Given our limited understanding of the biological underpinnings of OUD, one could assume that if society increased its levels of stress and depression, the epidemic could worsen due to more triggers for relapse (78).

The biological theory of OUD opens possibilities for multiple interventions at the physiological level. Emerging data suggests that nutrition may be a useful adjunct for biological (169) as well as social (170) intervention. Given the links between impaired gastrointestinal health and neuroinflammation (145), targeted nutrition interventions may ameliorate neuroinflammation,
which has been identified as a potential treatment for OUD (78). It has been argued that the microbiome is the link between person, public, and planetary health (184) and therefore we must consider environmental, psychosocial, and personal/nutritional factors implicated in gut dysbiosis. Much more research is needed on biological aspects of OUD that include nutrition-related factors which should consider the link between SES and access to food.

Policy Interventions

While no one single policy intervention on opioid addiction has proven to be highly effective, several promising proposals have been made. Institutional level strategies (i.e., hospital) such as updated prescription guidelines for emergency rooms have decreased number of patients discharging with a prescription opioid by nearly 40% and sustained 2.5 years after the intervention (185). If the opioid crisis in the US is to be “solved” it will require a multilevel initiative engaging all sectors of the healthcare system (186). Prescription drug monitoring programs (PDMPs) (187) share data across states and represent a policy tool targeted toward providers, the broadest level of intervention in the socio-ecological model (188, 189). It has been shown that PDMP implementation is associated with reduced doctor shopping for prescription opiates, but PDMP utilization is not uniform across states, and has not yet been integrated into all EMRs (190, 191). There is good evidence that collaborative efforts with private health insurers can be successful in promoting best practices in opioid prescribing (192). This includes better training of pharmacists to detect and discuss drug misuse with patients (193). In 2016, Ohio passed a law that requires pharmacists to review a patient’s PMDP history before dispensing a new controlled substance, encouraging denial to some patients and thereby taking a more proactive role in pain management (194). Additional policy level interventions and enforcement of current efforts will be critical.

Treatment Implications

A trauma-focused treatment model typically involves empathy, curiosity, and trust (195). The current paradigm for OUD treatment is typically centered on psychotherapy in individual and group settings, in addition to psychiatry. Skills for distress tolerance and managing negative affect appear to be critical for maintaining sobriety. Other treatment approaches which consider neuroscience may lead to targeted treatments and better outcomes. Meanwhile, a purely medical approach to treatment (e.g., MAT alone) often fails to consider the importance of the patient-clinician relationship in the recovery process (195). Targeted treatments for individuals who are at heightened psychosocial and biological risk may benefit from the inclusion of enhanced treatment protocols such as gut-focused nutrition therapy. “Holistic” approaches including nutrition is not widely accepted but have been growing in popularity in the private sector. Leading experts are consistently calling for “research into new treatments for OUD” (196) but nutrition therapy has lagged behind. It has been argued that failure to address nutritional conditions can severely undermine treatment (197). In Los Angeles, nutrition services are offered at less than a third of SUD treatment centers (198). Our work has shown educational and culinary interventions can be effective despite operational challenges (199). Nutritional protocols for OUD have been described elsewhere (200) and specific group education topics for SUD treatment have also been recommended (201).

Nutrition Interventions

Epidemiological research suggests that nutrient imbalance is a strong predictor of substance use and may be partially mediated by depression (202). Some authors have recommended dietary supplements for use in early recovery from heroin (203). It remains unknown how these supplements interact with MAT, and the reader is referred to a more comprehensive review (200). Methadone maintenance patients have received nutritional counseling aimed at reducing diet-related morbidity but a lack of measurable changes (e.g., weight) reduce the scientific salience (204). Meanwhile, nutrition services provided within the Veterans Affairs health care system have been associated with significant improvements in treatment outcomes (205). A small study demonstrated improvements in self-reported abstinence following nutrition education during alcohol treatment (206). The concept of nutrition education has been successfully introduced into recovery programs within the prison system as means of improving overall wellness (207, 208). Improved eating patterns and reductions in waist circumference have occurred following educational and environmental interventions in male residential treatment settings (209, 210). Gender-specific approaches for women including education around body image reduced eating disorder symptomatology (211). Women in residential treatment have expressed increased concern about their food choices during recovery (212). Taken together, the potential for use of nutrition as part of a BPS framework for OUD treatment appears underutilized and poorly documented.

Life Course Perspective

The Life Course Perspective (LCP) is not new to public health (213). The LCP puts a temporal element to the various factors in the BPS Perspective. LCP is a way of understanding human development and adaptation from an intergenerational approach considering all factors contributing to health outcomes, and how these factors accumulate over time. This concept has been described as a “biological embedding” of the environment and of one’s lived experiences (214, 215). In the LCP, environment includes access to health and social services, which is directly linked to SES as well as cultural norms within that context. LCP includes complex concepts such as epigenetics and is therefore a much broader way of understanding health. Transgenerational inheritance of addiction-like behavior appears supported by epigenetic mechanisms (i.e., environmental exposure) over genetic factors (107). Furthermore, epigenetic modifications acquired in one generation can be inherited by the next generation and can involve behavioral or social transmission (107), including the transmission of trauma (216).

The LCP considers multiple pathways contributing to disease, at the biological level (genetic/epigenetic) but also emphasizing how social ties influence health behavior and how these accumulate throughout the life course (217). Meanwhile, LCP
consider not only how disadvantage impacts health outcomes, but how cumulative advantage can play a role (218). In the case of OUD, social advantage may protect one from stress, or facilitate an individual receiving better treatment. LCP considers psychosocial mediators in the biological programing of health (219) and is therefore a major hub for recycling predictors of health outcomes in Figure 1.

Biopsychosocial Perspective

The BPS Perspective incorporates all of the factors and levels discussed in this paper and recognizes environmental, psychosocial, biological, as well as their mediating factors. This single cohesive framework considers the interdependency of the entire system, drawing its conceptual roots from socio-ecological models (188, 189) including Ecosocial Theory (23). The BPS Perspective suggests the risk factors and protective factors that influence substance-seeking behavior at the individual and population level, and how they may impact health outcomes. Of particular importance in the opioid crisis appears to be the mediating role of life stressors, and possibly the role of gastrointestinal health. While genetics cannot be changed, epigenetics and the microbiome are both potential intervention targets by way of nutrition, albeit much slower than medication, and therefore difficult to measure (behavioral outcomes vs. biomarkers). Meanwhile, the reductionistic approach to generating high quality evidence contributes to the absence of evidence for more complex approaches, such as those discussed herein. Addressing the opioid crisis from all perspectives discussed herein should be considered a public health priority. More research is needed to determine if nutrition can be helpful.

Future Directions

It will be important to identify aspects of an individual’s neurochemistry which are modifiable by epigenetic and microbial mechanisms. With strong evidence of overlapping pathways between drugs of abuse and food (220), it is surprising that food has not been investigated as a long-term modulator of reward pathways in humans. Meanwhile, authors from around the globe have suggested that nutrition interventions may be helpful in combating the opioid crisis (156, 198, 221). More evidence is needed before it will be recognized as a treatment modality. Specifically, it would be helpful to measure how nutrition interventions in early recovery can impact the gut microbiome, and how this can affect brain function (e.g., neuroinflammation) and thereby overall chances of recovery. With new measures and specific biomarkers of health status (e.g., allostatic load, microbiome, etc.), the BPS Perspective can be operationalized. This work may end up being conducted under the emerging field of “nutritional psychiatry” (222, 223). To date, gut-based nutrition interventions for OUD have not been investigated in humans but do appear to be timely.

CONCLUSION

A multifactorial problem that requires effective collaboration across multiple disciplines at multiple levels has been described. The future of multidisciplinary BPS work will necessitate an understanding of health as a dynamic and integrated system. It has been emphasized that the potential for nutrition to be utilized as one facet of a BPS approach may improve recovery outcomes. At a minimum, we should consider nutritional screening at intake in OUD treatment programs. Going forward, we need policies that address access to opioids and pain management. The overdose epidemic should be viewed through the lens of community impact. Paramount are the social determinants of health, particularly given associations between social disadvantage and the lifetime accumulation of stress and trauma, as well as how social factors impact opioid use (224, 225) and nutritional status (226, 227). What happens in early life has profound consequences in adulthood, and what happens in one generation may hold significance for future generations. To combat the opioid epidemic, we cannot ignore either the social or the biological determinants of health. This paper adds to the voice of other authors that have called for a “biopsychosocial revolution” linking science and humanism (228). It is time to advocate for an integration of social and biological disciplines in order to better address the opioid tragedy. Collaborative efforts and partnerships across disciplines will be critical, and the field of public health nutrition appears ripe for leading the way.

DATA AVAILABILITY

No datasets were generated or analyzed for this study.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

ACKNOWLEDGMENTS

DW would like to thank Dr. Christopher Evans from the University of California Los Angeles for his feedback on the manuscript.

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**Conflict of Interest Statement:** The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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