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Opinion

Microbiome First Approaches in Pain Prevention and Management

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Abstract

The Microbiome First Initiative aims to facilitate sustainable healthcare by focusing first and foremost on the human holobiont majority, the microbiome. Understanding how the human microbiome affects not only risk of disease but also human perceptions can help individuals thrive and pave the way for a healthy life course. Following a recent review of Microbiome First Medicine the context of health and safety, this present opinion article considers the role of the human microbiome, particularly the gut microbiome, on pain, sensory perceptions, and the prevention and multimodal management of pain. Microbial dysbiosis can be causative of some forms of immune-inflammatory and neurologic pain and the altered human microbiome can lock in the pain while at the same time interfering with analgesic/opioid therapies. Dysbiotic microbiota can make drug treatments less effective and with opioids, the microbes can significantly increase:

1. Opioid tolerance
2. The risk of addiction
3. The likelihood of withdrawal failure.

For these reasons, it is critical to move beyond simply thinking about the microbiome in dealing with pain to considering the microbiome as central in multimodal pain prevention and management strategies. The microbiome is key in any attempts to change physiology, metabolism, systems biology function, and receptor-based perceptions within the human body.

Keywords: Holobiont, Pain, Gut microbiome, Inflammation, Depression, Opioids, Addiction, Drug tolerance, Withdrawal, Probiotics, Prebiotics, Microbiome first, Human superorganism, Sustainable Healthcare

Abbreviations: NSAIDs: Non-steroidal anti-inflammatory drugs; NCDs: Noncommunicable diseases and conditions; CR: Colonization resistance; Staph A: Staphyloccocus aureus; PTX: Paclitaxel; CDC: Centers for Disease Control and Prevention; NIEHS: National Institute for Environmental Health Sciences

Introduction

The Microbiome First initiative is attempting to elevate awareness of the extent to which the human microbiome along with its majority of human genes affects all aspects of human development, health, disease and wellbeing. Including the microbiome in medicine, public health, prevention, nutrition, wellness, and therapeutics is essential if we are to open a path toward sustainable healthcare [1]. In some cases, the human microbiome may play an adjunct role in prevention and therapy while in many cases [e.g., colonization resistance against infections, prevention of noncommunicable diseases and conditions (NCDs)], it should be the first consideration. This opinion article describes the role of the microbiome in pain.

Human microbiota (including commensals and pathobionts) have a central role in pain because they can: cause pain, ablate pain, be damaged by pain medications, inactivate certain pain medications, predispose for opioid addiction, produce opioid tolerance, and affect the success or failure of opioid withdrawal. Given the fact that the human microbiome is not only a target for pain prevention and management but also affects all aspects of pain management, we can no longer afford to manage pain while

excluding the human microbiome. This article introduces types of pain and the factors that produce them. It also illustrates examples of the connections between the microbiome and pain and the opportunities to include the microbiome-based applications in pain prevention and relief.

Pain

Chronic pain is one of the most insidious conditions experienced across populations. According to a CDC report on the topic [2], it is one of the most common reasons for seeking medical care. Additionally, it restricts daily activity and can result in opioid dependence and reduced quality of life. A decade ago, pain was touted as a global health priority [3]. In a 2016 estimate by the CDC, 50 million adult Americans carried the burden of chronic pain [2]. Chronic pain rarely exists in isolation. There are frequent comorbidities that arise and increase the burden for those patients who are already dealing with pain. These additional comorbid conditions include but are not limited to depression, anxiety, sleep disturbances, fatigue/lack of energy, and neurocognitive changes [4]. Chronic pain treatment has led to significant problems with the use and misuse of opioids. The problem is significant enough that alternating therapeutics were recently suggested to avoid loss of productivity, addiction, and even opioid-related death [5-7].

The world of pain involves systems biology processes, sensing threshold, and emotions and can be divided into several categories based on location, cause, mechanism and duration (acute vs. chronic). Of the major categories and in keeping with the Rea et al. [8] and Guo et al. [9] reviews, nociceptive pain is usually the result of tissue injury. It is often further subdivided into visceral (a deep internal organ/tissue pain often as a result of damage) and somatic (pain receptors activated in a particular area such as skin, a particular muscle or skeletal region). Bladder or prostate pain would be an example of visceral pain while joint pain from arthritis would be an example of somatic pain. In contrast, inflammatory pain results from immune responses to infections, vaccinations or chronic noncommunicable diseases and conditions (NCDs) driven by inflammation. Infections and vaccinations most commonly result in inflammatory pain.

Finally, neuropathic pain is a category usually caused by nerve irritation or damage. Diabetic peripheral neuropathy would be an example of neuropathic pain [10]. As with the other examples of pain, microbiota can regulate neuropathic pain affecting both the initiation of pain and the thresholds of pain perception [11,12]. Neuropathic pain is considered among the most serious and challenging forms of pain to manage [13]. As Lin et al. point out [11], the power in gut microbiota as regulators of pain including neuropathic pain is that the microbes sit at intersections of immune, neural, endocrine, and metabolic signaling pathways. That complex network has both direct and indirect ways to affect neuropathic pain. The central position of the gut microbiome in the gut-brain axis makes it a preeminent target for pain management strategies.

The microbiome plays a role in virtually all aspects of pain (including initiation and cessation). Pathobionts are one of the primary causes of immune-inflammatory-related pain. One of the most painful infections is caused by the flesh-eating bacteria, *Streptococcus pyogenes*. Once it penetrates the barrier (e.g., skin), it can result in necrotizing fasciitis. The bacterium takes control of the body's pain sensing neurons, and this causes the infection to be more painful than it would be otherwise [14]. Numerous other bacteria can produce quite painful infections in different body locations [15]. For example, as described by Chiu et al. [16], *Staphylococcus aureus* (Staph A), a gram-positive bacterial pathogen, can cause painful skin infections while *Salmonella enterica* and *Escherichia coli* are responsible for painful gastrointestinal and urinary tract infections.

Staph A can also cause pain via pore forming toxins [17]. Gram negative bacteria, which carry lipopolysaccharide (LPS), can cause direct activation of the TRPA1 ion channel on nociceptors resulting in pain and can also cause signaling via Toll-like receptor 4 (TLR-4). Nociceptors also detect bacterial N-formyl peptides [16]. Fungal pathogens (*e.g., Candida albicans*) can induce calcium flux in nociceptors and viral pathogens also have some TLR routes to affect neurons [16]. Infectious (or septic) arthritis is a joint pain condition. A variety of pathobionts can be involved including the agent of Lyme disease (*Borrelia burgdorferi*) [18] and *Mycoplasma hominis* [19].

The airways are also a target for especially painful infection-related diseases. Bronchiectasis is a highly painful airway infection that often results in a chronic condition with lung scarring. It is also comorbid with asthma and can exacerbate an already challenging and painful experience for the patient [20]. While a number of pathobionts have been associated with bronchiectasis including some viruses, two bacteria are of particular interest for their association with disease severity: *Pseudomonas aeruginosa* [21] and Staph A [22], both having the capacity to form biofilms. It is important to recognize that when pathobionts are involved in pain-inflicting conditions that can become chronic, colonization resistance affords a natural and effective protection against pathobionts within the microbiome. For example, there are several combinations of commensal bacteria that work against carriage of Staph A including *Staphylococcus epidermidis* [23]. Using Microbiome First applications, we should never miss an opportunity to optimize front-line protection against dangerous pathogens [21].

Vaccinations most commonly resulting in pain appear to be

those with high ISAR scores. ISARs are inflammation-related solicited adverse reactions including local pain, redness, swelling or induration and systematic fever [24]. High ISAR scores are often indicative of a high immune reaction response to the vaccine [24]. Vaccination induced pain has been associated with autoimmune/inflammatory syndrome induced by adjuvants (ASIA syndrome). A recent example has been the cases of subacute thyroiditis resulting from the Sinovac Biotech SARS-CoV-2 vaccine [25] as well as from the Oxford-AstraZeneca, United Kingdom vaccine [26]. Examples of pain-associated acute disseminated encephalomyelitis (ADEM) have also resulted from a single dose of the SARS-CoV-2 mRNA vaccine (Moderna COVID-19 Vaccine, Moderna TX, Inc. USA) [27]. Bozkurt et al. [28] reviewed examples of cases of myocarditis with chest pain resulting from both of the mRNA vaccines from Pfizer-BioNTech and Moderna. Salmon et al. [29] detail five examples of vaccines that passed though safety testing; yet when they were administered, they produced inflammatory-autoimmune-pain syndromes. Two of the vaccine examples are the SARS1 Pandemrix vaccine and narcolepsy, and the human papillomavirus vaccine and complex regional pain syndrome.

With noncommunicable diseases it is clear that microbiome dysbiosis is a significant instigator of these diseases and conditions. This is all the more reason to use microbiome management as a pain reducing strategy. Virtually any NCD can have significant immune-inflicted pain associated with it because they are all driven by underlying inflammation. Additionally, most patients with NCD eventually develop additional comorbid NCDs [1]. Hence, a life-course pain reduction plan should include effective microbiome balance. As an example of the pervasiveness of painful NCDs, musculoskeletal NCDs (e.g., hip and knee osteoarthritis, rheumatoid arthritis, back and neck pain, and gout) number more than 150 different conditions [30] and more than 100 autoimmune conditions [31].

The topic of the capacity of the gut microbiome to regulate pain has been the subject of many recent reviews. Table 1 [8,9,11,32-51] illustrates and summarizes 23 of these review articles that detail a variety of aspects surrounding pain initiation, detection, biochemistry, and management. As captured among these reviews, there has been an explosion of research on this topic over the past five years. The good news is that the complexity of pain and its perception is largely being deconstructed by knowledge of the gut. As a result, factors controlling the microbiome's bi-directional signaling to the immune system, brain, neurological and endocrine systems are being laid bare and executive pathways determining the initiation and perception of pain are being revealed. Importantly, these review articles also detail the probiotic, prebiotic, and rebiosis strategies that have been used thus far in pain prevention and remediation. Examples are included that focus on pain associated with gastrointestinal issues (ulcerative colitis and irritable bowel), osteoarthritis, probiotics and headaches, post-surgical pain, neurologic and visceral pain, menopausal status, the risk-benefit role of opioids, the connections between microbiota and microglia activation, and gut microbiota as pertains to pain hypersensitivity vs. tolerance.

While a variety of microbiome studies are described within the review articles in Table 1, the most recent preclinical and clinical trials from the past 2-3 years are highlighted in Table 2 [52-71]. Several areas of activity are notable. First, pain in children (e.g., abdominal) seems to be an area where there is significant interest in the use of pre- and probiotics. Possibly this is because of the hesitancy to immediately prescribe opioids for children. The examples of recent preclinical and clinical trials show that a wide array of pain associated conditions can benefit from microbiome rebiosis. However, it is also clear that additional trials with larger numbers of patients and more standardized probiotic treatments will be helpful in guiding clinical applications.

Table 1: Examples of Recent Reviews on Microbiota, Pain, and Pain Management.

Scope of Review	Noted Effects/Findings	Reference(s)
Review of cannabinoids and the microbiome in pain	The review provides a well-designed schematic of the endocannabinoid system and the gut microbiota-involved pathways to regulate pain. Both are important contributors to pain regulation, although the interactions between the two are comparatively understudied. The authors suggest that prebiotics and probiotics can be used as adjunct therapies regarding pain management and that the microbiome itself is both accessible and adaptable as a route to better health.	[8]
Review of different types of pain, effect of a variety of probiotics, and mechanisms of microbiota regulation of pain as of 2019	This is a very comprehensive review on microbiota and mechanisms of pain regulation. It illustrates that ample evidence exists for the effects of the microbiome for several categories of pain (e.g., visceral, inflammatory, and neuropathic pain, as well as opioid tolerance). Less information was available for headache pain although some positive-effect studies with probiotics exist. Pain modification by microbiota can be direct and/or indirect.	[9]
Review article on childhood abdominal pain and different treatment strategies for childhood and adolescent abdominal pain. A section on trials with probiotics was included in the review.	Studies reviewed utilized *Lactobacillus reuteri*, *Lactobacillus* GG, *Bifidobacteria* species, *Bifidobacteria* and a *Lactobacillus* species, or a combination of *Bacillus coagulase* and a prebiotic. These were the most common and useful treatments. The authors concluded that while more comparative studies are needed, probiotics are a reasonable early intervention in pediatrics particularly for irritable bowel syndrome (IBS). Positive results with probiotics occurred to a lesser degree for functional abdominal pain disorders (FAPD) and to a lesser extent for functional dyspepsia (FD).	[32]

Review on postoperative pain and the gut microbiome	This is a thorough review covering the various effects of the microbiome on pain. The nature of pain surrounding surgery and recovery is detailed. Direct and indirect interaction with the nervous system is reviewed. The processes through which microbiota induce somatic pain and the probiotics that have been used to reduce pain are discussed. Additionally, the authors conclude that there is justification for targeted use of microbes and prebiotics to enhance the quality of perioperative analgesia and comfort.	[33]
Review on probiotics as adjunct for Ulcerative colitis bloating and pain	Studies with *Bifidobacterium*, *Saccharomyces boulardii*, and lactic acid-producing bacteria have shown promise. Additional range finding studies will be useful.	[34]
Review on animal models of visceral pain and the microbiome	This is a comprehensive review of various animal models for visceral pain with data on microbiota effects for 20 different visceral hypersensitivity procedures. It also describes microbiome assessment and manipulation using germ-free rodents, antibiotic, fecal microbiota transplantation and probiotics.	[35]
Review on microbiota and opioids	The review provides a comprehensive look at microbiota and their impact on social behavior. Additionally, it describes how opioids alter gut microbiome composition and how microbiota affect the development of antinociceptive tolerance and opioid-induced hyperalgesia.	[36]
Review on gut microbiome and osteoarthritis	The review considers microbiota and osteoarthritis (OA). It provides the pathways through which probiotics work to lesson OA and illustrates five different trials with probiotics and the impact on both disease outcomes and inflammatory markers.	[37]
Review on probiotics and amelioration of rheumatoid arthritis	The review describes the role of microbiota with rheumatoid arthritis (RA). Characteristics of six different categories of bacteria that initiate or prevent RA. Additionally clinical trials with probiotics are described. Probiotics including *Lactobacillus* casei and *Lactobacillus acidophilus* were found to be beneficial against RA.	[38]
Review of the clinical management of the microbiome in Irritable Bowel Syndrome	The authors describe the effects of irritable bowel syndrome (IBS) and recommends a multimodal treatment regime that includes probiotics. They point out that probiotics have had success with several parameters connected to IBS. But the same is not true for prebiotics alone to date.	[39]
Review of microbiota and somatic pain	The review discusses the transferability of colon sensitivity with IBS with the transfer of gut microbiota even across species.	[40]
Review of microbiota and spinal cord injury	The review includes a section on changes in gut microbiota that are associated with spinal injury and contribute to chronic pain. The authors conclude that remodeling of the gut microbiota appears to aid both neurological repair as well as pain reduction.	[41]
Review of the relationship between microbiota, microglia in the brain, the vagus nerve connection and pain.	The article presents information on how microbiota may influence microglia activation and control pain via this pathway.	[42]
Review on gut microbiota, immunity, and pain	The review details how gut microbiota work with the immune system to produce inflammation and visceral pain. It also describes the role of microbiota in opioid tolerance.	[43]
Review of the microbiome and regional pain syndrome	This review discusses the potential role for the gut microbiota as a potential biomarker for diagnosis, treatment, and clinical course prediction. Among the pathways considered are effects on the microglia, and other targets via microbial metabolites such as short chain fatty acids. Information is presented on beneficial effects from both prebiotics and probiotic bacteria.	[44]
Review of microbiota diet and hand osteoarthritis	The review focuses on obesity-related changes to microbiota as factors in hand osteroarthritis. Metabolites such as Trimethylamine-N-oxide (TMAO) are discussed as negative factors.	[45]
Review of the opioid system and microbiota dysbiosis	The review covers opioids and the gut-brain axis with some information on the effect of opioids on specific gut microbiota and also probiotic effects on opioid sensitivity/ thresholds.	[46]
Review of gut microbiota regulating neuropathic pain	The article describes the range of pathways through which gut microbiota can regulate neurologic pain. Included are numerous immunological, endocrine, and neurological pathways to regulate pain. Microbiota-based therapies including use of diet, antibiotics, fecal microbiota transplants are presented.	[11]
Review of urinary microbiome and Interstitial cystitis/bladder pain syndrome	The article suggests that the urinary microbiome changes with age and that *Lactobaccilus* content is related to menopausal status. However, these changes do not appear to be related directly to UTIs.	[47]
Review on migraine headache including gut microbiota	The review discusses several routes through which gut microbiota may directly and indirectly impact migraine headaches. Additionally, studies of potential benefits from probiotic administration are discussed including one study using a 14-strain probiotic mixture producing reduced frequency and intensity of headaches with less medication required.	[48]
Review of gut microbiota and pertinence in fibromyalgia	The authors describe recent metabolic analysis of fibromyalgia patients suggesting that they differ in microbiome composition compared with controls. However, it is unclear if the difference is causative. While microbiota can control pain, the authors concluded that more research is needed on the fibromyalgia microbiome before rebiosis approaches are recommended. Dietary recommendations remain a strategy.	[49]

Review on microbial compound and visceral pain	This review describes the mechanisms utilized by microbiota (commensals and pathobionts) to influence visceral pain perception. An emphasis is placed on discerning difference between transient and chronic pain. The range of microbiota products that affect the nervous system is discussed by category. The author concluded that microbial products can play a critical role in the regulation of chronic visceral pain.	[50]
Review on gut microbiota and visceral pain	The review covers visceral hypersensitivity and nociception to pain and presents prebiotic and probiotic results from both preclinical studies in mice and rats and six clinical trials.	[51]

Table 2: Examples of preclinical and clinical studies on the role of the microbiome in pain thresholds and pain management.

Study Group	Microbiota Involved	Effects	Key References
Recurrent abdominal pain in children	*Lactobacillus reuteri* DSM 17938 probiotic administration	Pain was less severe in the probiotic treatment group and the children had more days without pain during the study	[52,53]
Recurrent abdominal pain in children	*Lactobacillus rhamnosus* GG used in five trials reviewed	Reduction in both pain frequency and intensity in the probiotic treatment group	[54]
Recurrent abdominal pain in children	*Lactobacillus reuteri* DSM 17938 and *Lactobacillus rhamnosus* GG examined as probiotics	*L. reuteri* DSM 17938 singificanntly reduced pain intensity and increased days without pain. No effects were seen with *L. rhamnose* GG	[55]
Post-operative pain after upper limb surgery with peripheral nerve block	No preoperative manipulation. This was a comparison of microbiota associated with low vs. high pain.	In a comparatively small study, a major finding was that post operative analgesic consumption was inversely correlated with the Shannon index of Alpha diversity. Porphyromonas was associated with acceptable pain levels while a greater abundance of Lachnospira and Alistipes was observed in patients with unacceptable pain.	[56]
*Gut microbiota basis of chemotherapeutic-induced pain	Manipulation of gut microbiota in a mouse model of chemotherapeutically induced pain can promote or suppress inflammation-mediated pain.	Gut microbiotas are critical for the induction of or protection against chemotherapeutically induced pain.	[57]
*Probiotic formulation tested to alleviate chemotherapeutic-induced (Paclitaxel, PTX) peripheral neuropathy including pain	SLAB51 probiotic formulation evaluated in in vivo pain model for action on inflammatory mediators of pain.	The probiotic treatment reduced both the inflammatory markers in serum as well as the PTX-elevated neuropathic pain proteins in the spinal cord.	[58]
Probiotics to counteract chemotherapy (Paclitaxel) induced neuropathic pain.	Extracts of the probiotic mix DSF were used to examine the suppression of chemotherapeutic-induced, inflammation-mediated pain. DFS contains *L. plantarum* DMS24730, *S. thermophilus* DSM24731, *B. breve* DSM24732, *L. paracasei* DSM24733, *L. delbrueckii* subsp. Bulgaricus DSM24734, *L. acidophilus* DSM24735, *B. longum* DSM24736, *B. infantis* DSM24737.	The probiotic mix mechanistically works against the upregulation of Interleukin 8 (IL-8) by interfering with signaling. IL-8 is produced in response to sensitive neurons and contributes to the pain cascade.	[59]
Oral lesions and pain from orthodontic appliances	*Lactobacillus brevis* CD2 probiotic treatment	Significant reduction in the pain score.	[60]
Recovery from third mandible molar (tooth) extraction (surgery) evaluations using a randomized, double blind controlled pilot study.	Treatment group had one tablet two times a day containing a mixture of Levi *Lactobacillus brevis* CECT7480 (KABP-052) and *Lactoplantibacillus plantarum* CECT7481 (KABP-051) or placebo for the first post-intervention week.	Significantly reduced pain and few eating difficulties in the group receiving the probiotic.	[61]
Chronic widespread pain as often occurs in fibromyalgia from among a twin study	The stool microbiome was analyzed using 16S rRNA amplicon sequencing and amplicon sequence variants.	Alpha diversity was significantly lower in the chronic widespread pain group vs. the twin controls. The bacterium *Coprococcus comes* was significantly elevated in the group with chronic widespread pain. A causal role was not established.	[62]

Symptomatic Hand Osteoarthritis	This was a study analyzing the gut microbiome of the population from an area of China (a portion of whom had hand osteoarthritis). No microbiome manipulation was involved in this population study.	Low relative abundance of Roseburia but high relative abundance of *Bilophila* and *Desulfovibrio* was found in a population analysis of subjects of the Xiangya (China) Osteoarthritis Study	[63]
*Manipulated fecal microbiota transplantation was used between colitis induced mice and antibiotic treated recipient rats. The transplanted microbiota were manipulated to change donor microbiota.	Manipulated fecal microbiota transplants were used to determine how the thresholds of visceral pain were controlled by microbiota.	Visceral pain thresholds in the recipient rats were controlled by spectrum of bacteria transferred and their short chain fatty acid production profile.	[64]
Probiotics study in Ovariectomized (OVX) rats	Probiotic administration of *Lactobacillus intestinalis* YT2 was utilized.	The treatment alleviated menopausal symptoms including reducing pain sensitivity.	[65]
Probiotic treatment of pain associated with irritable bowel syndrome	*Lactobacillus acidophilus* strain administration	*Lactobacillus acidophilus* was found to modulate Intestinal pain and to induce opioid and cannabinoid receptors. This provides a potentially safer way to control pain.	[66]
Acyloxyacyl hydrolase is a host determinant that leads to microbiota dysbiosis that induces pelvic pain during interstitial cystitis. Mice with AOAH and deficient in it were examined for pain following microbiota transplants.	Fecal microbiota transplants were utilized.	Transplants from AOAH deficient mice to AOAH adequate mice produced pelvic pain. Fecal transplants in the reverse direction could protect against pelvic pain.	[67,68]
Lower disc herniation (LDH) as a result of inflammation is common cause of lower back pain	*Lactobacillus paracasei* S16	The probiotic elevates the anti-inflammatory response blunting the immune response that causes LDH. As a result, it protects against the development of LDH.	[69,70]
Effects of probiotics on migraines	A randomized double-blind controlled trial using a 14 strain probiotics mixture administered for 10 weeks in episodic migrainers and for 8 weeks in chronic migrainers. The probiotic mixture contained *Bacillus subtilis* PXN 21, *Bifidobacterium bifidum* PXN 23, *Bifidobacterium breve* PXN 25, *Bifidobacterium infantis* PXN 27, *Bifidobacterium longum* PXN 30, *Lactobacillus acidophilus* PXN 35, Lactob. delbrueckii ssp. bulgaricus PXN 39, *Lactob. casei* PXN 37, *Lactob. plantarum* PXN 47, *Lactob. rhamnosus* PXN 54, *Lactob. helveticus* PXN 45, *Lactob. salivarius* PXN 57, *Lactococcus lactis* ssp. lactis PXN 63, and *Streptococcus thermophilus* PXN 66.	There was a significant reduction in migraine attacks in the probiotic vs. placebo groups of both *episode* and chronic migraine patients. Additionally, the probiotic treatment groups (episodic and chronic) had less severity of attacks and less use of other drugs vs. the respective placebo groups. Ironically for the inflammatory markers measured, no treatment changes were noted despite the positive clinical outcomes.	[71]
*Designates preclinical animal studies. The remaining examples were clinical human trials.			

Microbiota And Analgesics: Opioid Response, Tolerance, Addiction and Withdrawal

A heavy reliance on pharmaceutical control of pain has several issues. Commonly used painkillers (opioids and non-steroidal anti-inflammatory drugs [NSAIDs]) are among the drugs known to damage the microbiome as discussed by Dietert [1]. While opioids are a category of drugs that have been used in pain management [72], they are also a drug category that has a significant opportunity to cause abuse [73]. This has most recently been seen with regards to fentanyl [74]. Recently, there is a search for multimodal pain management to reduce the reliance on opioids [75,76]. The gut microbiome plays essential roles both in the incentive salience end of drug reward behavior and in the pain of withdrawal response

as was recently reviewed by Ren and Loftipour [77] and García-Cabrerizo et al. [78]. Additionally, opioid tolerance is one of the features of a dysbiotic microbiome [79]. This contributes to ever increasing doses of opioids that are required to produce the pain-killing effect. It is part of the addiction cycle. There is evidence that rebiosis should be helpful in reversing opioid tolerance connected to microbiome dysbiosis. Zhang et al. [80] found that morphine tolerance established in germ free mice was able to be reversed using probiotics.

A second issue with pharmaceutical control of pain is that NSAIDs have been shown to damage the gut microbiome [81,82]. The specific damage impairs colonization resistance and creates increased susceptibility to *Clostridioides difficile* infection-induced colitis and dysregulates inflammation [83]. Even if microbiota are not used in a multimodal pain control strategy, the microbiome needs to be rebiosed following pharmaceutical therapy. Otherwise, there is a likelihood that the drugs will become less effective, more likely to become addictive and the microbial dysbiosis they create will put the patient at a greater risk of both infections and NCDs.

Conclusions

This opinion article provides both recent reviews and preclinical and clinical trials to illustrate the benefits of considering the microbiome at every step in the pain preventative and management process. The microbiome and, in particular, the gut microbiome exerts such a pervasive control over systems biology units (e.g., the microimmunosome, the gut-brain axis, the gut-bile axis, the gut-hepatic axis) and metabolism that efforts to manage chronic pain in the absence of managing the microbiome are far more likely to end in a reduced quality of life (either through ongoing pain, depression, and/or drug dependency). A concluding summary of four major benefits to be gained by putting the microbiome first in pain management is shown as follows:

1. Microbiome first action can be useful as a pain preventative. Because microbiota can regulate immune and neurogenic inflammation, there is an opportunity to stop neuronal activation and immune-inflicted tissue damage before lower back pain requires a surgical solution. This is what was found with lumbar injury and avoidance of the need for herniated disc surgery.

2. Inattention to the microbiome presents a long-term problem when it comes to pain. NSAID and opioid treatment for pain causes damage to the gut microbiome. If uncorrected, this creates a vicious cycle of trouble. There is an increase in drug tolerance (less effective drug action per dose) and for opioids there is a greater risk of addiction. Withdrawal is more difficult if the microbiome is in dybiosis. Additionally, the dysbiotic gut microbiome loses colonization resistance increasing the risk of serious pathobiont infections. There is also an increased risk for loss of gut barrier integrity and for the emergence of new NCDs. These new diseases will lead to increased pain and disease burden. None of these complications are necessary when appropriate attention is given to the microbiome.

3. Regular attention to the microbiome has benefits that include and extend beyond pain as an outcome. Better regulation of the body's immune system and inflammatory responses means that a lower prevalence of pain is likely over time. Having a better balance of receptor-driven perception of pain also means that there is a better chance to keep pain as an acute event rather than a lifelong chronic burden. It is a useful step toward sustainable healthcare.

4. Maintaining a healthy microbiome can reduce the comorbidities of pain. Because some NCDs like depression are very common comorbidities of chronic pain, managing the microbiome can help to eliminate these comorbidities. The gut as well as the gut microbiota are potent producers of neuroactive peptides. Balance among the gut microbiota produce improved neurological health. As a result, a healthy, managed gut microbiome enhances resiliency against pain-associated depression.

Conflict of Interest

The authors declare that there is no conflict of interest.

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