

# Pain Chronobiology and Epigenetic Regulation Nutrition, Nutraceuticals, Acupuncture

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## Abstract

The biopsychosocial model allows an evaluation of different parameters involved in chronic pain. There may, however, be simple non-iatrogenic strategies based on the physiology that can improve treatment outcome. Non-drug strategies as nutrition, nutraceuticals and acupuncture in addition to drugs take a special place in the management of critical situations where conservative treatment failed.

A therapeutic algorithm integrating chronobiology and the epigenetics factors considering the inter individual variability has been used for several years. The applied chronobiology also uses acupuncture strategies that associate the extraordinary vessels regulation, individualized points focussing on the typology of each, system regulator points, trigger points, auriculotherapy. Acupuncture is effective for the treatment of chronic pain and is therefore a reasonable referral option. Significant differences between true and sham acupuncture indicate that acupuncture is more than a placebo. Both principles of classic acupuncture and the latest scientific explanation of the underlying mechanisms explained above show that acupuncture involves central and peripheral mechanisms. Treating intestinal mucosa and microbiome involved in chronicity and drug response seems to be one of the points of the enhancing effect. This report analyses the published reports illustrating the basis of the multimodal model reasoning, which are retrieved and discussed in light of explaining the findings in clinical practice.

**Keywords:** Acupuncture; Chronobiology; Integrative pain medicine; Multimodal treatment; Nutrition

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## Introduction

The knowledge of biological and neurophysiological mechanisms of pain is enhanced, but still numerous treatment failures are observed in clinical practice. The biopsychosocial model allows an evaluation of all parameters involved but, investigation of what can be improved physiologically in all the parts with simple non-iatrogenic strategies is warranted. Non-drug strategies as nutrition, nutraceuticals and acupuncture in addition to drugs take a special place in the management of many critical situations or failed treatments. The association of nutrition and nutraceuticals with pain development and perception, requires the knowledge of appropriate nutrition for patients with cancer, the role of obesity in pain chronification, the microbiome involved in pain, and the specific role of soy, omega-3 fatty acids, curcumin, and polyphenols on inflammatory and degenerative painful diseases as well as on opioid tolerance [1]. Chronobiology and acupuncture

are two very different medicines, but they meet at one criterion: the importance of the notion of time and of the temporal structure of physiological and pathological phenomena. The apparent stability of the organism actually covers a multitude of biological rhythms, creating a temporal map for each organism, adapted to the influences of its environment. Experiments are now carried out in human medicine, and the applications of chronobiology in pathology, pharmacology and therapeutics are numerous; the practitioner can integrate the time factor into his daily practice in order to optimize the treatment of his patient. In acupuncture, cyclical phenomena constitute a basis of this medicine, and it is possible to treat the patient according to the years, the months, the days and even the hours of the day; these data are combined in a chrono-acupuncture therapeutic disc. The use of the time factor in medical practice allows for a planning of predictable high-risk times for the body, enhanced biological

monitoring at the right time, and improvement of the desired effects and decreasing its side effects for the patient. The term “nutraceutical” was coined from the combination of nutrition and pharmaceutical in 1989 by dr Stephen De felice. It refers to a food, or part of food providing health benefits, including prevention and treatment of a disease.

## Physiological and Neurophysiological Steps

Understanding the role of integrative medicine requires assessment of nociceptors, microbiome and intestinal mucosa, Cyp450 involved in metabolism and interaction, chronobiology, the neuroendocrinology clock of the system, and day night rhythms analysis. There are biological, psychological, and environmental factors predisposing for central sensitization. The peripheral sensitization of the primary nociceptors depends on intra and extra cellular homeostasis. This bidirectional adaptability of nociceptors, close to homeostasis sustains the hypothesis of acupuncture and anti-inflammatory effect of nutrition on the peripheral and central sensitization. Certain nutriment can modify the expression of the genes by leading a set of stable but potentially reversible modifications of the DNA, without modifications of the genetic code, called ‘epigenetic modifications’. This mode of regulation, which gives to the cell a system of ignition or locking of certain genes, is also sensitive to the environmental exposures [2,3]. Central sensitization in chronicity shows activate mechanisms involving opioids receptors, microglia and low-grade inflammation. Functional neuroimaging techniques made the study of both the neuroanatomical and neurophysiological responses associated with acupuncture possible. Changes in brain structure and cortical function are associated with many chronic pain conditions. Most studies report changes in common areas involved in pain modulation, including the prefrontal cortex (PFC), and pain-related pathological changes in the PFC can be reversed with effective treatment. Functional neuroimaging studies, documented brain responses in cortical and subcortical regions, including activation in the sensorimotor cortical and deactivation in the limbic-paralimbic-neocortical network with acupuncture treatment. These brain areas are associated with a pain matrix responsible for modulating the sensation of pain and affective pain perception. Questioning these fundamentals of neurophysiology results in the following hypothesis: by revalidation of the main chronobiological rhythm, sleep, food, vicious circle involved in pain sensitization are regulated. The revalidation of intestinal mucosa, microbiome, and sustaining liver function, act on drug metabolism and side effects. The diagnostic steps are integrated with the chronobiology purpose and the epigenetics factors involved in the inter individual variability [3,4]. Genetic variations [1,3-7] may modulate the answer to treatment as does the inter-individual differences in the bacterial flora of the human digestive tract. Based on these observations we developed a treatment algorithm combining acupuncture, pharmaconutrition, including the natural compound, palmitoylethanolamide (PEA), a glial modulator and peroxysome-activated receptor alpha agonist, vitamin D and nutritional rehabilitation close to drugs.

## Integrative Pain Medicine Involving Nutrition and Nutraceuticals in Addition to Acupuncture

Integrative medicine is the integration of all appropriate health care strategies and disciplines for the patients’ benefit. Commonly used analgesics include the nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and local anesthetics. But their use can have problems like idiosyncratic reactions, gastrointestinal bleeding, dependence liability, and so on. There is also wide patient to patient variation in their efficacies. Besides, the management of neuropathic pain and chemotherapy-associated pain still remain challenging. The need for developing better and safer analgesics is thus still valid. The role of phytochemicals for developing many modern medicines cannot be overestimated. Aspirin and the opioid analgesics are directly from plants. For developing new-generation analgesics, plants are more significantly relevant as many nociceptive ion channels are modulated by some common phytochemicals such as capsaicin, piperine, eugenol, and menthol. Other plant products such cannabinoids act on the endocannabinoid receptors to modulate pain pathways and thus can be beneficial in chronic pain. There have been ongoing attempts to target these ion channels and the cannabinoid receptors with semisynthetic derivatives of these phytochemicals [3,4].

At every stage of the life the sustaining strategy and association of nutrition and nutraceuticals take a special place particularly with the actual life society where food is less convivial than 30 years ago and where the danger and effects of the time on intake food is known. An anti-inflammatory dietary improves many functions of the body and is involved in many chronic situations. Intestinal mucosa and leaky gut can be at the frontier of drug metabolism and side effects of treatments involved in the vicious circle of peripheral and central sensitization. Moreover, the effect of drugs, stress and epigenetic factors on the metabolism leads to enhancing side effects. The strategies to sustain these vicious circles close to sensitization of pain, failure of drugs treatment, and enhancing side effects, by nutrition and/or nutraceuticals close to acupuncture could improve all the underlying parts and solve pending questions of treatment.

Actually, two main dietaries are emerging as improving numerous parameters:

1. Mediterranean dietary
2. Okinawa dietary food map

Fundamental research and clinical observation shows that the most effective approach is a simple treatment based on common sense more effective. In common sense remembering Hippocrates “let thy food be thy medicine and the medicine be thy food. The ideal dietary approach for patients on opioids should include increased consumption of fiber and fluids (at least eight glasses daily unless contraindicated), in conjunction with physical activity, with abdominal exercises in bed or moving from bed to chair if the patient is not able to walk. Patients are encouraged to eat more high-fiber foods such as fruits (grapes, prunes, peaches, and apples), vegetables (e.g., squash, broccoli,

carrots, and celery), and 100% whole-grain cereals, breads, and bran. Nevertheless, fiber intake should occur several hours prior to or following the drug administration to mitigate a reduction in the bioavailability of certain drugs [7]. It is also known that more than 3 prescribed drugs could lead to less efficacy and more side effects. Nutraceuticals act like drugs but in a way of sustaining and improving the physiological revalidation. They can, when associated to drugs, improve metabolism and efficacy lowering doses and preventing some side effects involved in the vicious circle of chronic disease or pain chronicity. It is less well recognized that proton pump inhibitors cause vitamin B12 deficiencies as well as magnesium deficiencies and dysbiosis in the gut. Each of these conditions may be associated with increased pain. Processed foods and drugs such as proton pump inhibitors, NSAIDs, antibiotics, steroids, and hormones can adversely affect the microbiome [3,4]. The peripheral sensitization of the primary nociceptors also depends on the intra and extra cellular homeostasis. The bidirectional signaling can be activated by the inflammation that it modulates. Acupuncture also increases brain activity in regions closely associated with a wider pain matrix responsible for modulating both the sensation and affective pain perception [2]. Acupuncture strategies associate the

extraordinary vessels regulation, individualized points focused on the typology of each, system regulator points, trigger points, auriculotherapy.

Treating intestinal mucosa and microbiome involved to chronicity and drug response seems to be one of the points of the enhancing effects.

## Conclusion

The expectation is that this nutritional approach and acupuncture will further clarify the role of precision medicine in the treatment of pain, acting as an essential, integrated, non-pharmacological strategy and as an aspect of multidisciplinary treatment for chronic pain. Acupuncture in this multidisciplinary is a multimodal pain regulator [2,8,9]. The therapeutic and post effect are augmented by the cellular physiological rehabilitation. A strategy that integrate pharmaco nutritional and acupuncture with analgesics shows as described in the literature, a better response and tolerance of the treatment, a dose reduction and a significant improvement of the vicious circle induced with chronic pain. With the algorithm integrating clinical to fundamental knowledge, used for 30 years, in clinical practice, revalidations after treatment failures are observed.

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