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Review

Neural Mechanisms of Hypnotic Analgesia

Giuseppe De Benedittis *

Department of Neurosurgery, University of Milan, Italy; E-Mail: giuseppe.debenedittis@unimi.it

* **Correspondence:** Giuseppe De Benedittis; E-Mail: giuseppe.debenedittis@unimi.it

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Abstract

There is increasing evidence demonstrating that hypnosis could be effective in the down-modulation of pain sensation in both acute and chronic pain states. In the neurophysiological context, recent evidence has deciphered, to a certain extent, the mystery of pain relief upon hypnosis. It is probable that hypnotic suggestions of analgesia are able to modulate pain processing at multiple levels and sites within the central nervous system (CNS). At the peripheral level, hypnosis may modulate the nociceptive input through the down-regulation of the stimulation of A delta and C fibers and reduction of sympathetic arousal. At the spinal level, sensory analgesia occurring during hypnosis has been demonstrated to be linearly associated with the reduction in the nociceptive flexion (RIII) reflex, a polysynaptic spinal reflex. At the supraspinal cortical level, neuro-imaging and electrophysiological studies have demonstrated that hypnotic suggestions of analgesia could directly modulate both sensory and affective dimensions of pain perception, and the affective dimensions exhibit more significant reduction compared to the sensory ones. Moreover, highly hypnotizable subjects possess stronger attentional filtering abilities in comparison to the low hypnotizable subjects; this greater cognitive flexibility of the former might result in better focusing and diverting the attention from the nociceptive stimulus as well as in better ignoring of the irrelevant stimuli in the environment. Cognitive control processes are associated with a "supervisory attentional system" which involves fronto-temporal limbic cortices.

Multiple hierarchical pain control systems functioning during hypnotic suggestions of analgesia, demonstrating specific patterns of peripheral and central activation associated with the hypnotic state and with the processing of hypnotic suggestions, provide a novel description of the neurobiological basis of hypnotic analgesia.

Keywords
Hypnosis; hypnotic analgesia; mechanisms; review

1. Acute and Chronic Pain: Definition and Magnitude of the Problem

Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" by the *International Association for the Study of Pain* [1].

Pain is the most common reason for physician consultation in most of the developed countries [2]. It is a major symptom in several medical conditions, and may interfere with the quality of life and general functioning of a person [3].

Pain that persist for a long duration is referred to as "chronic" or persistent pain, while the pain that resolves within a short period of time is referred to as "acute". Chronic pain is defined as the pain that persists or recurs for greater than three months or beyond the expected period of healing [4].

Pain is the main reason for visits to an emergency department in greater than 50% of the cases [5]. In 30% of family practice visits, the presence of pain is there [6]. Epidemiological studies have reported that 10.1%–55.2% of the people in various countries experience chronic pain [7].

According to a global-level epidemiology report by Tsang et al. [8], there was a 37.3% age-standardized prevalence of chronic pain conditions in the previous 12 months in developed countries, 41.1% in developing countries, and an overall prevalence of 38.4% globally.

1.1 Pathogenetic Pain Phenotypes

Pain may be broadly categorized into nociceptive pain and neuropathic pain. Nociceptive pain is caused by the stimulation of sensory nerve fibers that respond to the stimuli approaching or exceeding the harmful intensity (nociceptors). Nociceptive pain may be classified on the basis of the mode of noxious stimulation (*e.g.*, inflammatory or cancer pain).

Neuropathic pain, on the other hand, is caused by damage or disease affecting any part of the nervous system involved with bodily feelings (the somatosensory system) [9]. Neuropathic pain may be experienced in CNS disorders (such as spinal cord injuries, multiple sclerosis, and certain strokes) or peripheral neuropathies (such as herpes zoster and diabetic neuropathy). It is also common in cancer, as a direct consequence of cancer on peripheral nerves (e.g., compression by a tumor) or as a side effect of chemotherapy (chemotherapy-induced peripheral neuropathy), radiation injury, or surgery [10].

1.2 Economic Burden of Pain

In addition to worsening the quality of life of those who experience it, pain also presents an economic burden, both for the suffering individuals and the health care systems.

Individual costs comprise direct costs (e.g., medical care payments) and indirect costs (e.g., paying for the activities these people are no longer able to perform). Among the indirect costs, loss in work productivity constitutes the majority of the overall costs associated with pain [11]. Furthermore, in several countries, the workforce is in the continuous process of aging, which could lead to a major economic impact when these individuals would require early retirement owing to their painful health conditions.

1.3 Access to Treatment for Pain Relief as a Human Right

According to the international human rights law, countries are required to provide pain treatment medications as a part of their core obligations under the right to health. Despite the importance and magnitude of the problem and the existence of several inexpensive and effective pain relief treatments, inadequate treatment of pain, particularly that of chronic pain, is widespread [12]. Tens of millions of people worldwide continue to suffer from moderate to severe pain each year, without relief. Failure to undertake reasonable steps for ensuring that the people who suffer from pain have access to adequate pain treatment may represent a violation of the obligation to protect against cruel, inhuman, and degrading treatment.

The *International Association for the Study of Pain* [13] advocates that receiving pain relief should be recognized as a human right, chronic pain should be considered a disease in its own right, and pain medicine should receive the full status of a specialty.

1.4 Addressing Pain beyond Medications

Primarily, chronic pain is not a biomedical problem, and is, therefore, not easily resolved using a single simple biomedical treatment approach. Instead, chronic pain is a biopsychosocial problem that requires the consideration of and treatments that address the several biological, psychological, and social factors that may contribute to its severity and the impact caused by it [14].

Owing to their limited efficacy, simple pain medications are useful only in 20%–70% of the cases [15]. Moreover, there are frequent significant side effects of medications, such as the recent opioid epidemic in USA [16], which is the most common reason for people shifting to the use of complementary and alternative medicine [17].

The experience of pain may be dramatically influenced by cognitive modulation [18].

Among all the cognitive interventions for pain modulation, hypnosis may be the most effective in clinical and experimental pain [19-21]. A few studies have addressed the important issue of the long-term effects of hypnotic analgesia. There is a consensus among outcome studies which suggests that analgesic effects of hypnosis are long-lasting and are maintained over time [22-26].

2. What is Hypnosis?

The term "hypnosis" refers to a state of consciousness that involves focused attention and reduced peripheral awareness, which is characterized by an enhanced capacity for response to suggestion [27]. This term also refers to the procedure through which the afore-stated state is induced. It is possible to modify physiological, cognitive, and affective processes, as well as behavior, during a hypnotic trance. Hypnotic state and hypnotic phenomena may be induced by another person (therapist) or by oneself (self-hypnosis). The subjective experience of hypnosis is characterized by focused attention, absorption capacity, a high degree of authenticity (experienced as real), involuntariness ("it happens by itself"), and cognitive/perceptual flexibility [28, 29].

Hypnosis has been an elusive concept for science for a long time due to the lack of objective neurobiological markers for the state of trance. However, persistent advances in the field of neuroscience in the last few decades (largely because of the introduction and refinement of sophisticated electrophysiological and neuro-imaging techniques) have opened up a 'bridge of knowledge' connecting the classical neurophysiological studies with the psychophysiological studies of cognitive, emotional, and sensory systems [28, 30]. These neuroscience studies have provided novel insights into the neural basis of hypnotic experience. Furthermore, an ambitious area of research focusing on mapping the core processes of psychotherapy and their underlying neurobiology has emerged recently. Research related to hypnosis has offered powerful techniques for the isolation of psychological processes in ways that allow their neural bases to be mapped. The *Hypnotic Brain* [31] could serve as a tool to approach the neurocognitive questions, and the cognitive assays may, in turn, provide insight into the neural bases of hypnosis. This cross-talk shall enhance related research and clinical applications.

While the recent advances in neuroscience have undoubtedly contributed to unraveling the nature of hypnotic reality [29, 32], i.e., its neuro-cognitive structure, hypnosis is also being increasingly recognized by the international scientific community as a valid and flexible physiological tool for the exploration of the central and peripheral nervous systems. This might be a real Copernican revolution in this field [28].

3. Neural Correlates of Hypnosis

Current research on hypnosis comprises two major areas [31]: (a) *intrinsic research*, i.e., the line of research concerned with the functional anatomy of hypnosis per se, in the absence of specific suggestions referred to as 'neutral hypnosis' or 'default hypnosis', and on the neurophysiological mechanisms underlying the hypnotic experience in dynamic conditions, and (b) *instrumental research* (or extrinsic studies), which involves the use of hypnosis and suggestion for studying a wide range of cognitive and emotional processes, as well as for creating 'virtual analogs' of neurological and psychopathological conditions, to elucidate their basis, and eventually positively alter the manner in which they are treated.

An array of novel electrophysiological and neuro-imaging techniques has contributed to the significant advances in the knowledge regarding hypnotic phenomena, including functional neuro-anatomy of neutral hypnosis. These techniques include electrophysiological studies (*e.g.,* bispectral analysis), neuroimaging (e.g., single-photon emission computed tomography (SPECT), functional magnetic resonance imaging (fMRI), and positron emission tomography (PET)),

advanced neuro-imaging (*e.g.,* real-time fMRI and brain–computer interface), and neurofeedback [31].

EEG studies. Hypnotic states and hypnotic responding (including hypnotic analgesia) are frequently accompanied by an increase in the theta band power and changes in the gamma activity [14, 33]. These oscillations are thought to play a critical role in both recording and recall of declarative memory and emotional limbic circuits and are possibly the mechanistic link between theta (and perhaps gamma) oscillations and hypnosis. Theta oscillations, which are concomitant with the changes in gamma activity, may underlie and facilitate certain hypnotic responses. These findings appear to have important implications for understanding the effects of hypnosis as well as for enhancing the response to hypnotic treatments [33].

In addition to its contribution to validating and defining the state of trance, neuroscience has enabled differentiation between the altered states of consciousness and the ordinary states of consciousness. Bispectral electro-encephalographic analysis, a sophisticated and complex version of spectral analysis, has proved to be effective in differentiating between the subjects that are awake and the ones that are in trance, based on the bispectral (BIS) index [28].

Neuro-imaging studies. Several studies involving neuro-imaging (fMRI and PET) [28, 34-39] have contributed to creating a map of Regions of Interest (ROI) in the brain during 'neutral' or 'default' hypnosis (i.e., hypnosis in the absence of any specific suggestion), including the occipital cortex (the part of the brain involved in visualization processing, which is crucial for the induction and the experience of hypnosis), thalamus, anterior cingulate cortex (ACC), inferior parietal cortex, precuneus (part of the brain that normally mediates imagery and self-awareness) [36], and dorsolateral prefrontal cortex. Perhaps, soon the researchers would be able to sketch a 'Neurosignature' (functional neuro-anatomy) of hypnosis. Furthermore, findings of certain neuro-imaging studies suggest a potential anatomical (morphological and volumetric) basis for hypnotizability, linking variations in the rostrum of the corpus callosum to differences in the attentional and inhibitory processes [40].

4. Mechanisms underlying Hypnotic Analgesia

Hypnotic analgesia represents a significant paradigm of the manner in which neurophysiological and neuropsychological research has contributed decisively to a better understanding of the mechanisms underlying the multidimensional pain control in trance. Given the complex multidimensional nature of the pain experience, it is probable that hypnotic analgesia involves multiple mechanisms for pain modulation.

There is strong evidence suggesting a broader conceptual scheme, postulating that dynamically distributed processing in large-scale networks, possibly operating in parallel, might be integrating and causing modulation at different neural levels and sites of the pain experience.

The combination of all evidence suggests that the concurrent activation of this network of central and peripheral neural structures might constitute the "neurosignature" of the hypnotic pain modulation.

The research on the neurophysiological mechanisms underlying hypnotic analgesia has focused mainly on the peripheral and spinal mechanisms of nociception. However, the activation of these mechanisms is neither necessary nor sufficient to produce the perception of pain [41]. Pain is perceived when complex integrated cortical and subcortical (supraspinal) systems are engaged,

with or without the presence of nociception, and it is possible to relieve the pain by disengaging or interrupting these systems. As a consequence, the main mechanism underlying pain relief by means of hypnosis is a top–down rather than a bottom–up mechanism [34].

Although a number of supraspinal sites have been reported to be involved in the perception of pain, the most consistent areas identified across different imaging studies are the thalamus, the primary and the secondary somatosensory cortex (S1 and S2), the anterior cingulate cortex, the insula, and the prefrontal cortex [41, 42].

4.1 Supraspinal Mechanisms

EEG–ERP Studies. Evidence that the differences in attention levels may account for hypnotic depth and individual differences in hypnotizability has been provided with traditional EEG rhythms, event-related potentials, and 40 Hz and gamma EEG activity [18, 28, 33]. The alteration in stimulus perception may be a secondary effect with respect to the allocation of attentional resources.

There is increasing research demonstrating that the magnitudes of different brain oscillation patterns are associated with the response to hypnotic inductions and suggestions [33]. It has also been demonstrated that hypnosis is associated more with theta oscillations, while hypnotic responding has been demonstrated to be associated with changes in the patterns of gamma oscillations (with potential increases, decreases, or changes in the timing of gamma oscillations), depending on several factors including the suggestions provided [33].

Laser-evoked potential (LEP) experiments have demonstrated that hypnosis may significantly reduce pain and the LEP N2-P2 complex amplitudes compared to the control condition [43]. These findings corroborate the hypothesis that hypnosis inhibits afferent nociceptive transmission; the physiological mechanism underlying hypnosis may involve the influence of sub-cortical gating processes on the cortical activation, which underlies the decreased subjective pain perception and the LEP modulation reported by the subjects under hypnosis.

Valentini and co-workers [44] studied whether the hypnotic suggestion of sensory and affective hypoalgesia (down condition) or hyperalgesia (up condition) could differentially influence the subjective ratings of laser-induced pain and nociceptive-related brain activity in high and low hypnotically-suggestible individuals. The authors observed a significant hypnotic modulation of pain intensity and unpleasantness in the highly suggestible patients and P2 modulation in the up and down conditions, suggesting a top-down modulatory effect on both evoked and induced cortical brain responses induced by selective nociceptive laser inputs. These studies provided evidence in favor of higher efficacy of hypnotic analgesia in highly hypnotizable subjects in experimental pain, indicating that the “high hypnotizables” might possess an enhanced ability for focused attention (or dis-attention) to information and activity controlled by what is referred to as the pain matrix cerebral areas. The reduction in the N2-P2 complex upon hypnotic induction might have been a result of modulation of pain matrix activity, particularly that of the ACC (the brain area that plays a primary role in generating the vertex complex).

Taken together, these studies suggest that clinical hypnosis could play a key role in maximizing both behavioral and neurophysiological responses, as hypnosis is a cognitive phenomenon that affects central nociceptive processing. Furthermore, these studies are supportive of greater

cognitive flexibility (*i.e.,* the subjective capacity to shift from one "state" to another) of the high hypnotizables compared to the low hypnotizables [28].

Neuro-imaging studies. Neuro-imaging techniques have contributed in a decisive manner to reveal the putative mechanisms of cognitive modulation of pain, including hypnotic analgesia. In a pioneer study using SPECT, De Benedittis & Longostrevi [45] observed a significant decrease in regional cerebral blood flow (rCBF) in the primary sensorimotor cortex (S1) during suggestions of hypnotic analgesia only in the highly hypnotizable subjects, which was possibly associated with selective neural inhibition.

The turning point in the field of neuro-imaging studies on hypnotic analgesia is represented by the pivotal studies conducted using PET by a Canadian team led by Pierre Rainville. The first one among these studies [46] demonstrated that hypnotic manipulation of the degree of negative affective resonance (unpleasantness) elicited by a nociceptive stimulation in a group of volunteers concomitantly induced corresponding changes in the activities of the brain structures (such as increased/reduced activation of the Anterior Cingulate Cortex, ACC) involved in the coding of motivational-affective component of pain. No change was observed in the activity of the primary sensorimotor cortex (S1), which is involved in the processing of sensory-discriminative component of the nociceptive stimulus. The extraordinary selectivity of hypnotic suggestion to differentially manipulate the two main components of the painful experience was documented in a pioneer study, which reported a marked linear correlation between the intensity of negative affective resonance, as suggested in the hypnosis, and the level of ACC activation. The study was followed by other research works by the same group as well as by Belgian researchers [38, 47], which corroborated and extended the results of the afore-stated study, suggesting that the ability of hypnosis to differentially modulate the different aspects of pain perception is not rigid, structural, and unidirectional, and rather dynamic and dependent on the structure and formulation of the hypnotic suggestions.

Brain imaging studies have also revealed increased activity in several regions of prefrontal cortices and the brain stem during hypnotic analgesia [38, 48]. Furthermore, increased connectivity between the ACC and the mesencephalon was observed in the peri-aqueductal grey (PAG) region [49]. This activation was consistent with the putative activation of the descending pathways involved in pain regulation.

In an fMRI study, painful stimulation in the normal alert state resulted in cerebral activation in a network encompassing cortical and subcortical areas of the brain (i.e., the ACC, premotor, dorsolateral, prefrontal, primary somatosensory and bilateral insular cortices, thalamus, bilateral striatum and brainstem, and the what is referred to as the Pain Matrix), while the same stimuli perceived under hypnosis failed to elicit any cerebral activation [30].

A review of functional neuro-imaging studies on pain perception during hypnosis [35, 50] indicated that hypnosis-induced modifications in pain perception are associated with functional changes in several ROIs, including the cingulate (mainly ACC) as well as the prefrontal, insular, and pregenual cortices, the thalamus, and the striatum. The ACC appears to be the key target in the process of reducing pain perception, regardless of the nociceptive stimulus applied, emphasizing the critical role of ACC in hypnosis-induced modification in the sensory, affective, behavioral, and cognitive aspects of nociception.

According to the theories of hypnosis, one characteristic of the hypnotic procedures is the inhibition of afferent nociceptive transmission. This inhibition may be explained by the dramatic

decrease observed in the activity within the thalamus under hypnosis [49]. The thalamus has also been demonstrated to correlate with the pain perception threshold, while the activation of the midline area (i.e., the posterior cingulate cortex) correlates with the intensity of stimulation and ACC with the unpleasantness of the stimulation [30].

It is becoming increasingly clear that hypnosis is able to effectively modulate not just the motivational-affective component of pain, rather also the sensory-discriminative one (which is further directly linked to the intensity of the nociceptive stimulation), although to a lesser extent. These findings confirm the great cognitive-perceptual flexibility mediated by trance, and would certainly exert a significant impact in the clinical context. The hypnotic modulation in pain intensity causes changes in pain-related activity mainly in the primary somatosensory cortex (S1), while the modulation of pain unpleasantness induces changes mainly in the anterior cingulate cortex (ACC), with the anterior (mid) cingulate cortex possibly modulating both sensory and affective components of pain [38, 51].

4.2 Spinal Mechanisms

Hypnotic analgesia may also be dependent on the activation of the descending inhibitory systems that specifically modulate the spinal transmission of the nociceptive input [52]. The involvement of these systems during hypnotic suggestions of analgesia was demonstrated in a few electrophysiological studies that reported that hypnosis leading to a significant reduction in the amplitude of the nociceptive flexion reflex (R-III), which is believed to be linearly correlated to the intensity of perceived pain [53, 54], and the effect was proportional to the extent of hypnotic suggestibility. There is limited knowledge regarding the details of these mechanisms, with the exception of the modification in synaptic transmission in spinal reflex pathways by descending signals from the brain, which is thought to be an important factor [18, 41, 55].

4.3 Autonomic and Peripheral Mechanisms

There is increasing evidence that in addition to spinal and supraspinal mechanisms, hypnosis also modulates the activity of the autonomic nervous system (ANS) and possibly the peripheral nervous system (PNS) as well. The sympatho-vagal interaction of the ANS during trance was investigated for the first time by De Benedittis *et al.* [56] through the spectral analysis of the heart rate variability signal (RR interval). The authors demonstrated that hypnosis modulates the RR interval by shifting the balance of the sympatho-vagal interaction toward an increased parasympathetic output, concomitant with a reduction in the sympathetic tone. The effect correlated positively with hypnotic susceptibility.

It has also been demonstrated [57] that the heat pain threshold assessed with thermal stimuli is significantly elevated during hypnosis, suggesting that hypnosis may down-regulate the neuronal inflow from the stimulation of A delta and C fibres. A recent study [58] assessed whether a focal glove hypnotic hand anesthesia could induce thermal changes within the area of hypnotic protection. There was a statistically significant difference in the temperature variation induced by the analgesic glove within the hand, wrist, and distal forearm on the glove side, compared to the proximal forearm and control side. Hypnotic glove analgesia provided significant changes in skin temperature within the protected areas.

In summary, the current evidence strongly supports the existence of multiple hierarchical pain-control systems during hypnotic suggestions of analgesia at different levels and sites within the nervous system [18, 23]. At the peripheral level, hypnosis may modulate the nociceptive input by down-regulating the stimulation of A delta and C fibers and reducing the sympathetic arousal, which is relevant for inducing and maintaining certain chronic pain states. At the spinal level, hypnosis probably activates the descending inhibitory systems by reducing the nociceptive R-III reflex, parallel to self-reported reduction in pain. At the supraspinal cortical level, neuro-imaging and electrophysiological studies have demonstrated the ability of hypnotic suggestions of analgesia to directly and selectively modulate both sensory and affective dimensions of pain perception (the latter exhibiting greater significant reduction compared to pain). Furthermore, the highly hypnotizable subjects possess stronger attentional filtering abilities compared to the low hypnotizable subjects, and this greater cognitive flexibility might result in better focusing and diverting attention from the nociceptive stimulus as well as in better ignoring the irrelevant stimuli in the environment.

Neuropsychological mechanisms underlying hypnotic analgesia are possibly diverse, and include factors related to the reinterpretation of the meanings associated with pain as well as the factors related to the reduced pain intensity; the latter may result either from dissociative mechanisms or from the mechanisms associated with focusing on the alternative or reduced sensations. Certain factors, in turn, are accompanied by modulation at cortical levels, such as in the case of modulation in the activity within the ACC and not in the S1 cortex during the reinterpretation of meanings. Other factors relate to the endogenous circuitry that descends to the brain stem and spinal levels, inhibiting nociceptive transmission within the cells of origin of the ascending pathways and modulating motor and autonomic responses [59].

Taken together, these data support the notion that cognitive (hypnotic) modulation of pain causes dramatic alterations in the cortical Pain Matrix [18, 23]. This complex network may represent the 'Neurosignature' of the hypnotic modulation of pain (De Benedittis, 2003)[18]. However, hypnosis is not a panacea and is unlikely to serve as a stand-alone therapy in the treatment of a variety of chronic pain syndromes, including inflammatory and neuropathic pain. Given the multifactorial nature of chronic pain, a multimodal approach, which includes hypnosis as well as pharmacotherapy (such as NSAID, tricyclic antidepressants, and antiepileptic drugs), is often the preferred and the most appropriate treatment for pain control [22, 23].

4.4 *Hypnosis Modulates Empathy for Pain*

Brain responses to pain experienced by oneself vs. pain viewed in other people indicate consistent overlap in the pain processing network, particularly the anterior insula, thereby supporting the view that pain empathy relies partly on the neural processes engaged by self-nociception [60].

A recent study demonstrated that inducing analgesia through hypnosis leads to decreased responses to both self and vicarious experience of pain [60]. The activations in the right anterior insula and amygdala were markedly reduced when the participants received painful thermal stimuli following hypnotic analgesia on their hand, and also when they viewed pictures of others' hands in pain. Hypnotic modulation of pain responses was associated with differential recruitment of right prefrontal regions involved in selective attention and inhibitory control. These findings

provided renewed support to the notion that self-nociception is involved during empathy for pain and demonstrated the potential of using hypnotic procedures for modulating higher-level emotional and social processes [60].

5. Conclusions

One of the oldest medical applications of hypnosis was pain control, the effectiveness of which, although known for quite some time now, has received indisputable confirmation at the level of evidence-based medicine quite recently. Increasing evidence has been suggesting that hypnosis could be effective in the down-modulation of pain sensation in both acute and chronic pain states. Hypnotic analgesia represents a significant paradigm of the manner in which neurophysiological and neuropsychological research has decisively contributed to a better understanding of the mechanisms underlying the multidimensional pain control in the state of trance.

Recent studies on hypnotic analgesia are rather convergent and strongly supportive of multiple hierarchical pain control systems during hypnotic suggestions of analgesia at different levels and sites within the nervous system, thereby providing a cognitive modulation of the Pain Matrix.

Author Contributions

GDB wrote the manuscript and reviewed the final manuscript.

Competing Interests

The Author has declared that no competing interests exist.

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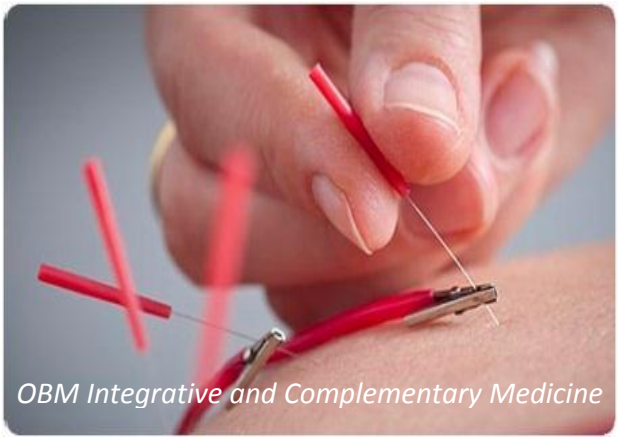

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