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REVIEW ARTICLE

Therapeutic Potential of Ultrasound Neuromodulation in Decreasing Neuropathic Pain: Clinical and Experimental Evidence

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Abstract: ***Background*:** For more than seven decades, ultrasound has been used as an imaging and diagnostic tool. Today, new technologies, such as focused ultrasound (FUS) neuromodulation, have revealed some innovative, potential applications. However, those applications have been barely studied to deal with neuropathic pain (NP), a cluster of chronic pain syndromes with a restricted response to conventional pharmaceuticals.

***Objective*:** To analyze the therapeutic potential of low-intensity (LIFUS) and high-intensity (HIFUS) FUS for managing NP.

***Methods*:** We performed a narrative review, including clinical and experimental ultrasound neuromodulation studies published in three main database repositories.

***Discussion*:** Evidence shows that FUS may influence several mechanisms relevant for neuropathic pain management such as modulation of ion channels, glutamatergic neurotransmission, cerebral blood flow, inflammation and neurotoxicity, neuronal morphology and survival, nerve regeneration, and remyelination. Some experimental models have shown that LIFUS may reduce allodynia after peripheral nerve damage. At the same time, a few clinical studies support its beneficial effect on reducing pain in nerve compression syndromes. In turn, Thalamic HIFUS ablation can reduce NP from several etiologies with minor side-effects, but some neurological sequelae might be permanent. HIFUS is also useful in lowering non-neuropathic pain in several disorders.

***Conclusion*:** Although an emerging set of studies brings new evidence on the therapeutic potential of both LIFUS and HIFUS for managing NP with minor side-effects, we need more controlled clinical trials to conclude about its safety and efficacy.

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1. INTRODUCTION

According to the International Association for the Study of Pain, pain is defined as a "disgusting sensitive or emotional sensation associated with real or potential tissue damage" [1] with sensory, emotional, cognitive and social components [2]. This association considers that pain becomes a chronic condition when it exceeds the average period for lesion recovery, which might be three months [1]. Chronic pain is one of the most common symptoms in several diseases [1] and may also occur after surgical intervention [3].

Neuropathic pain (NP) is a chronic pain disorder occurring after damage to the nervous system, either central or peripheral [1] that may affect 6-7% of the population [1]. A wide variety of medical conditions may develop NP, such as diabetes mellitus, viral infections (HIV and post-herpetic neuropathy), and fibromyalgia, among many others [1,4]. Some of these medical conditions are listed in Table **1** [5].

NP is often associated with peripheral nerve damage but may also have a central origin, as occurs after a stroke affecting somatosensory pathways [4] (Table **1**). However, some studies have questioned if the source of NP is central or peripheral [4]. Brain regions involved in central NP are the thalamus, the basal ganglia, the frontal lobe, the internal capsule, and the occipital lobe [4].

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Table 1. Medical conditions presenting with NP according to the international association for the study of pain.

Central Neuropathic Pain	Peripheral Neuropathic Pain
• Spinal cord injury • Brain injury • Post-stroke pain • Multiple sclerosis	• Trigeminal neuralgia • Peripheral nerve injury • Polyneuropathy • Postherpetic neuralgia • Radiculopathy

Independently of its origin (central or peripheral), several brain regions may be associated with pain modulation and processing. Pain reduction (due to the placebo effect) is associated with reduced activity in the thalamus, the insula, the somatosensory cortex, and mid-cingulate regions [6]. Other studies suggest a role for the dorsolateral prefrontal and anterior cingulate cortices, the hypothalamus, the periaqueductal gray matter, and the rostral ventromedial medulla [6].

Pain interventions may be challenging since, beyond its pathophysiological mechanisms, contextual (physical, psychological, or social) factors may influence pain, causing placebo and nocebo effects [7]. Regarding the placebo effect, it is lower using non-invasive techniques [7], like ultrasound, and may be reduced by magnetic peripheral neuromodulation [8].

Some studies suggest that 66-75% of a treatment effect for pain modulation may be associated with contextual factors [7], so this should be taken into account in both clinical trials and the clinical practice, where those factors may improve a treatment response [7] but may also yield false positive/negative results. Thus, some interventions might either cause or reduce a placebo effect altering the outcome of pain treatments.

Despite its exogenous nature, pain modulation by contextual factors involves some neurotransmitters, including opioid, cannabinoid, and dopaminergic systems [7]. Some authors suggest that the association between physical activity and NP requires an increased peripheral level of substance P that may alter the dorsal root ganglion (DRG), causing NP [9]. Experimental models of NP show that nerve damage increases substance P expression [10], supporting this hypothesis.

For all those reasons, NP management is difficult because of its several presentations, affected areas, and underlying mechanisms [11]. Thus, 60% of NP patients may be refractory to pharmacological treatment [1].

Despite some challenges, progress in the understanding of the pathophysiology of NP is spurring the development of new diagnostic procedures and personalized interventions, which emphasize the need for a multidisciplinary approach to the management of NP. The field of neuromodulation is increasing and has shown promising results for NP treatment using different tools, including ultrasound.

Besides the poor result with the current treatment armamentarium, we consider that neuromodulation is a promising field to explore derived from the results so far obtained. In this review, we aimed to analyze the therapeutic potential of low-intensity (LIFUS), and high-intensity (HIFUS) focused ultrasound for managing NP.

2. METHODS

This narrative review includes clinical trials, animal models, reviews, case reports, and conference papers ob-

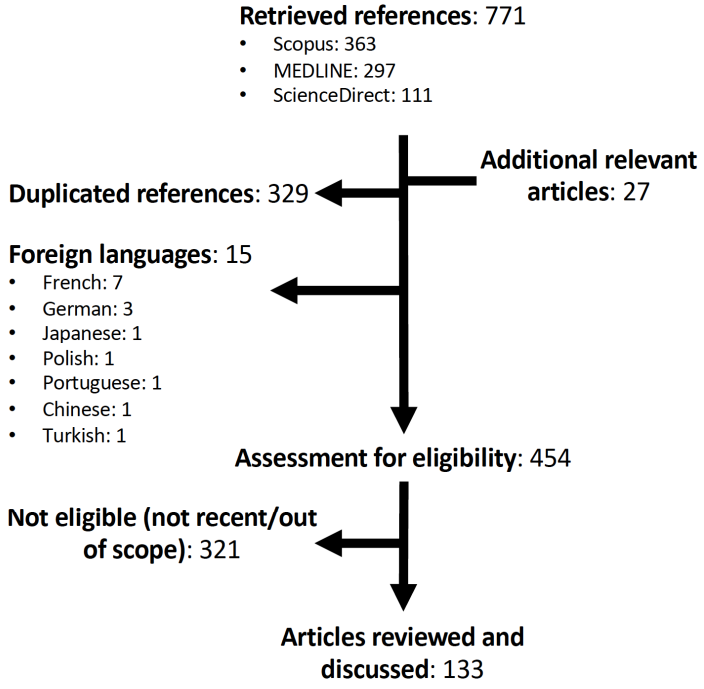

Fig. (1). Application of inclusion and exclusion criteria to define selected articles for this review.

tained from three main scientific bibliographic database repositories (MEDLINE, ScienceDirect, and Scopus). Inclusion criterion comprised records retrieved with the MeSH terms "ultrasound [title/abstract] and (neuromodulation [title/abstract] or neuropathic pain [title/abstract])". Exclusion criteria were: 1) language different from English or Spanish (unless English translations were found), and 2) articles not describing medical/biological applications of ultrasound (including imaging, diagnosis, and development of medical devices) or its mechanism of action. Studies testing FUS application in pain disorders (both clinical and experimental) were prioritized. This methodology is based on previous recommendations [12, 13] and is depicted in Fig. **1**.

3. DISCUSSION

3.1. Medical Applications of Ultrasound

Ultrasound is composed of mechanical waves whose frequency lies above the human hearing range, limited to 100-20,000 Hz [14, 15], and extends up to several gigahertz [16]. Sonic waves may propagate faster in soft tissues (1500 m/s) and bone (3500 m/s) as compared to air (330 m/s) [14], allowing ultrasound to interact with biological systems.

Five main parameters influence ultrasound: carrier frequency, peak intensity, duration, pulse repetition frequency, and duty cycle [17]. Combining these parameters may yield different results, so its standardization is an important factor for the achievement of a more reliable application [16] in the medical setting.

The thermal and mechanical effects of ultrasound could provide the basis for the therapeutic use of ultrasound in clinical areas. Therapeutic applications for ultrasound were tested for the first time in the late 1920s [16]. Focused ultrasound (FUS) was developed back in 1935 [11, 18], and its application to neuroscience began a few years later.

The first application of FUS to the brain of experimental animals was reported in 1943 [18] with limited success; in neurosurgical experiments, FUS produced significant damage to the scalp, the skull and the meninges [18].

FUS comprises an array of transducers [15] that concentrate energy at a single point [14]. These arrays may reach several targets simultaneously [19] and allow them to perform non-invasive neurosurgery [11] or neuromodulation.

There are two main modalities for FUS application: pulsed or continuous [14]. In pulsed FUS, ultrasound is delivered by short pulses reducing its thermal effect [14, 15] diminishing damage to nearby non-targeted structures. FUS has enough spatial lateral resolution (1-2 mm) [14, 20] to modulate a single brain region such as the mouse motor cortex [21-24], the macaque amygdala [25] or the human thalamus [26, 27] allowing a selective modulation. Some apparatuses show a spatial resolution similar to that obtained using radioneurosurgery techniques [28].

In medicine, ultrasound has been traditionally used as a diagnostic imaging tool [14, 29-41]. It is also useful for procedure guidance in surgery, anesthesiology, interventional radiology, and several medical specialties [42-54]. Additionally, it is also useful as imaging guidance for electrode implantation for electrical neuromodulation [55-63]. Some studies show that LIFUS intensities producing neuromodulation are similar to those used routinely for clinical purposes [15, 20]. The maximal ultrasound intensity recommended for diagnostic procedures is 190 W/cm^2 [15], which overlaps with therapeutic HIFUS (above 100 W/cm^2 [14, 15]) and exceeds LIFUS intensities (0.5-100 W/cm^2 [15]).

FUS therapies for neuroscience are challenging but possible and currently in use for several disorders, including NP. However, its efficacy, safety, and mechanism of action deserve further discussion.

3.2. Ultrasound Neuromodulation

According to the International Neuromodulation Society, therapeutic neuromodulation is defined as "the alteration of nerve activity through targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites in the body" [64]. Thus, neuromodulation represents the "selective activation or suppression of neuronal function in targeted brain regions" [65]. Several methods are available for this purpose, including transcranial magnetic stimulation (TMS), electric acoustic stimulation, deep brain stimulation, and FUS, among others [14, 66].

The neuromodulatory effect of ultrasound was observed for the first time in 1929 [16]. Its potential has been described since earlier studies showing that its application to the mouse motor cortex evokes muscle responses [66]; recent studies have replicated those findings [19, 67, 68]. This indicates that FUS may stimulate the nervous system, although inhibition of synaptic activity has also been suggested.

It is considered that FUS intensity determines the excitatory or inhibitory nature of its effect [17] although this remains to be demonstrated; however, its frequency may also be important to modulate its effect. Some studies have shown that using 350 kHz ultrasound elicits tail movements at lower acoustic intensities compared to 650 kHz when applied to the rat brain somatomotor area [69]. At lower intensities, high frequencies (2 MHz) produce a conduction block in peripheral nerves [28]. This effect involves an increase in temperature (41-45 ºC) and the inactivation of sodium channels [28]. Unmyelinated axons are more susceptible to this effect [70].

In human patients, FUS stimulation of the primary somatosensory cortex generates contralateral tactile sensations [66]. Those effects are accompanied by activation of several brain regions as observed by blood oxygen level-dependent (BOLD) magnetic resonance imaging (MRI) [66], suggesting that FUS increases neuronal activity. In another study, unfocused ultrasound applied with diagnostic equipment to the motor cortex of healthy volunteers increased the amplitude of TMS-induced motor-evoked potentials compared to placebo [71], which is consistent with a stimulatory effect.

It could be suggested the vascular system mediates the effect of FUS on BOLD signals. Some studies have shown that LIFUS increases regional cerebral blood flow [72]. Oxygenated and deoxygenated hemoglobin concentrations correlate with FUS-induced brain activation [72], supporting

this hypothesis. However, it should be considered that these mechanisms are coupled to each other through nitric oxide synthesis and glutamatergic signaling, and thus, increased excitatory activity in neurons enhances cerebral blood flow.

When applied to the human primary somatosensory cortex (3 W/cm^2), it evokes somatosensory potentials [15]. Depending on its parameters, LIFUS (100 MHz) spatial resolution may achieve 7.5 μm [15] although the experimental conditions for this result were not described in detail. Other studies suggest that it may achieve a focal volume of 0.161 mm^3 [73] in soft tissues like the brain. This allows stimulation of single neurons in the salamander retina [15]. In that system, LIFUS stimulation of the retina is faster than that obtained using light [15, 74]. The neuromodulatory effect of LIFUS may be observed 60 min after a 40-s stimulation and is reversible [14, 25].

Despite its high spatial resolution, LIFUS might stimulate non-targeted regions since it may be reflected by the skull [25]. However, some studies have shown that activation of non-targeted brain regions after LIFUS application is more likely because of their mutual connectivity [25, 75]. However, interference by the skull should always be considered.

Thus, several studies suggest an excitatory effect of FUS on the nervous system. Still, inhibition may also occur, especially when GABAergic neurons are activated. A detailed description of its mechanism of action might be helpful to explain these apparent discrepancies.

3.3. Mechanism of Action

3.3.1. Low-intensity Focused Ultrasound

LIFUS intensity is within the 0.05-100 W/cm^2 range [15, 16]. Its mechanism of action is not completely understood [14, 72], but it involves both thermal and non-thermal (mechanical) effects [66, 76].

3.3.1.1. Acoustic Startle Reflex

Startle reflex is the most common of all reflexes and is suggested to perform a protective role to avoid possible threatens [77]. It may be elicited by strong unexpected acoustic, tactile, or vestibular stimuli and bilaterally activates several muscle groups [77]. After the application of a mechanical force, it is dependent on mechanoreceptor activation [77].

Some studies have suggested that the FUS effect on the brain is a consequence of an acoustic startle reflex [14, 78]. LIFUS stimulation (0.34-4.2 W/cm^2 I_{SPTA}) of the mouse visual cortex produces neuronal activation in the auditory cortex [72, 78], but those regions do not connect to each other. Chemical deafening reduces LIFUS-induced motor responses [78], and bilateral damage to the auditory nerve reduces LIFUS-induced cortical activation [72]. Those results suggest that a startle reflex underlies the neuromodulatory effect of FUS. Still, it may also involve acoustic energy propagation through the skull and reverberations inside its cavity [72].

Further studies support the hypothesis of FUS-induced startle reflex. Some studies show that LIFUS (20 mW/cm^2 I_{SPPA}) may activate the guinea pig primary auditory cortex from several positions in the head [79]. This effect disappears by removing cochlear fluids or after bilateral auditory nerve transection [79].

These studies support the hypothesis that FUS effects occur by stimulating the auditory system, indirectly affecting several brain regions leading to motor responses; however, other studies show that this assumption is not entirely correct.

Some investigations show that the FUS effect is not dependent on auditory activation, since it is present in genetically deaf mice [25, 80]. Also, LIFUS application (2.3-4.6 W/cm^2 I_{SPPA}) to the primary auditory cortex or the inferior colliculi [72, 81] inhibits auditory-evoked potentials, showing that LIFUS does not activate acoustic responses under these experimental conditions. However, it does not imply that ultrasound could not activate acoustic responses. This effect may last between 30 min and one month in most animals [81], indicating that FUS modulation remains long after acoustic stimulation.

In awake rats, LIFUS (2.3-14.9 W/cm^2 I_{SPPA}) stimulation of auditory areas does not elicit movements in the tail, the limbs, or the whiskers [82], suggesting that activity in those regions induces no motor activation. The neuromodulatory effect of LIFUS may occur *in vitro* [15, 83], so it is not always explained by an auditory mechanism.

Together, several studies show that the FUS mechanism of action lies beyond acoustic stimulation, although a startle reflex component is also possible. Thus, it may be concluded that FUS may induce a mechanical activation of the auditory system, that FUS itself may suppress this effect and that its neuromodulatory activity involves several other mechanisms [72].

3.3.1.2. Mechanical Modulation of Neuronal Activity

Ultrasound may induce electric currents through the piezoelectric effect [14, 18]. This effect may occur in bone tissue, although it might be weak [84]. Conversely, electrical pulses can produce mechanical vibrations [18]. According to some computational studies, the application of a mechanical stimulus to an axon induces an electric pulse that may alter an action potential [75].

Mathematical modeling suggests that LIFUS may activate sodium, calcium, and potassium channels [85], and might produce action potentials in neurons [85]. The application of a mechanical force improves electrical transmission through a damaged axon, which might be associated with nerve regenerating [75] and remyelinating [86] effects elicited by FUS.

LIFUS stimulates action potentials and synaptic activity through a non-thermal effect on ion channels [15] (Fig. **2**), and it is also affected by the thermal effect [87]. Some authors suggest that FUS mechanical force activates sodium and potassium ion channels in brain cells [14, 66], altering membrane polarization. Behavioral responses to LIFUS are preserved in thermosensitive ion channel knock out *C. elegans* [15, 17] but knocking out mechanosensitive channels abolishes those responses [15, 17]. These results may include

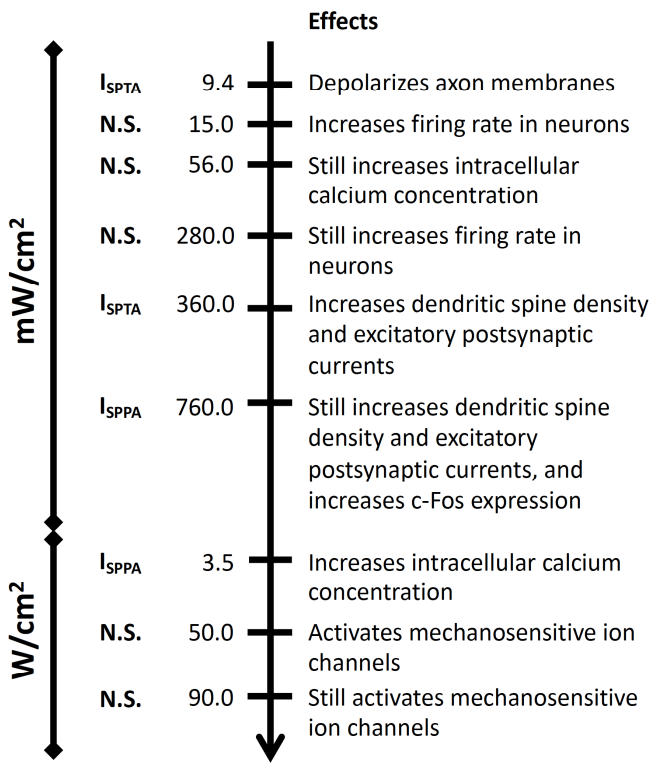

Fig. (2). Some effects of LIFUS at the cellular level. Most results are consistent with a stimulatory effect, although inhibition of synaptic activity has also been suggested. N.S., not specified.

a direct flexoelectric effect, which might occur in both myelinated and unmyelinated axons [75]. This effect consists of a spontaneous polarization in dielectric materials subjected to a mechanical gradient [75].

Some studies suggest that LIFUS (50-90 W/cm^2) activates mechanosensitive ion channels (Fig. **2**) through acoustic streaming [87]; this mechanism represents the sound-induced movement of fluids [88]. However, it occurs at high ultrasound intensities (2002 W/cm^2 I_{SPTA} [88]), so its therapeutic relevance remains to be determined.

Other studies show that ultrasound waves (9.4 mW/cm^2 I_{SPTA}) depolarize axon membranes generating action potentials [89] (Fig. **2**). Experiments using voltage-sensitive dyes and calcium imaging show that LIFUS (3.5 W/cm^2 I_{SPPA}) facilitates somatosensory-evoked potentials and increases intracellular calcium concentration [90] (Fig. **2**). Also, LIFUS (360-760 mW/cm^2) activates the cerebral cortex as measured by c-Fos expression [91, 92] (Fig. **2**) and electroencephalography [86]. Further studies agree with this excitatory effect [24, 85, 93].

However, some studies found that LIFUS (17.1 W/cm^2 I_{SPPA}) may reduce motor [94] and somatosensory-evoked potentials [27, 95], suggesting an inhibitory effect on neuronal activity [27, 72]. Some studies show that FUS either enhances [96] or reduces [25, 65] brain activity as measured by BOLD MRI.

Those discrepancies may arise from the different methodologies involved [72]. Still, it is also possible that LIFUS generates a bimodal effect [14, 17]. Some authors suggest that LIFUS reduces neuronal activity and that its excitatory effect involves the acoustic startle reflex [14]. Other studies suggest that lower FUS intensities are excitatory. In contrast, higher FUS intensities are inhibitory [17], but, to the best of our knowledge, no consensus exists.

Modulation of a brain circuitry might lead to paradoxical results; for example, inhibition of inhibitory neurons would produce an excitatory response. Thus, the analysis of single neurons might help to explain the actual effect of FUS on neuronal activity. However, performing electrophysiological studies is challenging since FUS vibrations may interfere with the recording electrodes [14].

Despite this limitation, some researchers have achieved those recordings [83, 87, 97]. LIFUS (15-30 mW/cm^2) increases the firing rate of CA1 hippocampal neurons by inhibiting K^+ currents [83] (Fig. **2**); this effect involves an increased frequency, duration, and amplitude of spontaneous action potentials [83]. Also, LIFUS (280 mW/cm^2) may increase the firing rate or retinal ganglion neurons (Fig. **2**); this effect is proportional to ultrasound intensity [74].

LIFUS may also change neuronal morphology [93]. LIFUS (360 mW/cm^2 I_{SPTA}) increases dendritic spine density and excitatory postsynaptic currents in hippocampal neurons [91] (Fig. **2**). These effects are related to an increased expression of the GluN2A subunit of the glutamatergic NMDA receptor [91] but may also involve a mechanical effect [93]. Studies showing that ketamine, an NMDA receptor antagonist, reduces LIFUS-induced (56 mW/cm^2) increased intracellular calcium levels [98] further support the involvement of glutamatergic neurotransmission.

Some authors suggest that the excitatory activity of FUS is mediated by a mechanical effect [14], causing intramembrane cavitation [15, 17]. This mechanism varies across cell types [85]. Intramembrane cavitation consists of the formation of gas microbubbles that grow and collapse within biological membranes [15, 17]. Cavitation is more likely to occur at low ultrasound frequencies [28]. It is considered that these mechanisms modulate membrane polarization [14]. This mechanism may occur in soft tissues using mechanical pressure above 1.9 MPa, although this threshold is frequency-dependent [17].

However, most neuromodulation studies use mechanical pressure below 0.6 MPa when studying the brain [17]. Thus, the relevance of cavitation for LIFUS excitation of peripheral nerves has been debated [15]. Some studies suggest that cavitation may reduce neuronal excitability [7]. This mechanism may cause a hyperpolarizing change of >100 mV in membrane potential, although it has not been demonstrated by electrophysiological recordings [17].

Several studies show that LIFUS modulates ion channels through mechanical effects leading to neuronal excitation. This might lead to either excitatory or inhibitory responses depending on the phenotype of the excited neurons. This effect might also involve glutamatergic neurotransmission and synaptic plasticity. Also, some studies suggest that FUS may modify gene expression of ion channels [66].

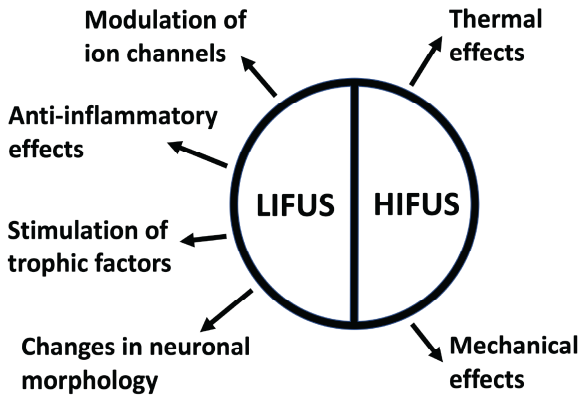

Fig. (3). Some mechanisms of action for LIFUS and HIFUS. LIFUS effect is basically neuromodulatory and neuroprotective, while HIFUS exerts tissue ablation through thermal and mechanical effects.

3.3.1.3. Cell Protective Effects of Ultrasound

LIFUS modulation of ion channel function is relevant in both health and disease but, when tissue damage occurs, inflammation may contribute to neuronal dysfunction or death, leading to aberrant manifestations such as NP. Thus, control of inflammatory processes is vital to achieve an integral therapeutic strategy.

LIFUS (30 mW/cm^2) reduced lipopolysaccharide-induced inflammation [16]. LIFUS (0.56-98 W/cm^2) elicits an anti-inflammatory effect reducing tumor necrosis factor (TNF)α and interleukin 1α levels [16, 20]. Its maximal effect is observed within 2 h after treatment and lasts up to 48 h [20]. Its mechanism of action involves T cell activation and acetylcholine signaling [20], suggesting that neuromodulatory and anti-inflammatory LIFUS' effects are intermingled. LIFUS also modulates cyclooxygenase expression and prostaglandin synthesis [16]. The anti-inflammatory effect is greater using LIFUS than using HIFUS [16] (Fig. **3**).

The anti-inflammatory effect of LIFUS may preserve neuron integrity and function after tissue damage, but additional mechanisms may be helpful. LIFUS modulates the activity of neurotrophic factors (Fig. **3**), including brain-derived neurotrophic factor, vascular endothelial growth factor, and glial-derived neurotrophic factor [15, 16]. It increases the expression of brain-derived neurotrophic factor [11, 72] and may increase hippocampal neurogenesis [11]. Modulating vascular endothelial growth factor may improve tissue revascularization of damaged tissue [16], increasing the supply for oxygen and nutrients and reducing a lesion.

Those mechanisms are relevant for inflammatory disorders causing cell death and leading to NP, such as multiple sclerosis. LIFUS (1.2 W/cm^2) does not reduce demyelination but accelerates spontaneous remyelination in a pharmacologic mouse model of multiple sclerosis [86]. This might impact electrical transmission; in fact, LIFUS (0.99-28.2 W/cm^2 I_{SPTA}) increases conduction velocity in peripheral rat nerves [99]. However, its therapeutic action through this mechanism may be questioned since spontaneous remyelination is not observed in human patients as much as it occurs in mice.

The remyelinating effect of LIFUS suggests that it either reduced oligodendrocyte death or increases their proliferation. Indeed, LIFUS may modulate cell proliferation and differentiation by stimulating transcription factors and protein kinases [16]. It may stimulate the proliferation of skin fibroblasts through ERK signaling and may also promote osteoblast and mesenchymal cell differentiation [16]. It remains to be determined if a similar effect occurs for oligodendrocyte precursors.

3.3.2. High-intensity Focused Ultrasound

In general terms, HIFUS utilizes intensities above 100 W/cm^2 [14, 15] (Fig. **2**) but may reach 10,000 W/cm^2 [16]. It has been used to produce controlled brain lesions in primate models since 1942 [14, 100]. In the 1950s, its use for neurosurgery was tested in experimental models by lesioning the thalamus and the internal capsule in cats [18, 100]. Its application to reduce pain started in the mid-1950s [100].

Early studies in humans were performed in the 1960s, reducing tremor and rigidity in Parkinson's disease (PD) [18]. Brain tumors were treated with HIFUS in the 1940s [18] and 1970s [100]. Soon after, radiosurgery was preferred over HIFUS because of its technical limitations [18, 101], including lacking intraoperative guidance for its application [18,101], requiring an extensive craniotomy to deliver ultrasound waves [11, 101] and an important temperature rise damaging surrounding tissues [18, 102].

This is a fundamental issue since its thermal effect may result in tissue ablation [66] (Fig. **3**). Early studies showed that gray matter ablation requires higher ultrasound energy than white matter ablation [18, 100], which might favor its side-effects. Blood vessels are also more resistant than nerve tracts [18].

Nowadays, those limitations have been circumvented [102]. HIFUS ablation may be considered an alternative to both conventional neurosurgery and radiosurgery [102]. However, more studies are needed to better determine its efficacy and side-effects.

Its mechanism of action is more clearly elucidated than that of LIFUS. HIFUS ablation occurs thorough two main mechanisms [6] (Fig. **3**). It is frequency-dependent: mid frequencies (650 kHz) produce thermal ablation, whereas low frequencies (220 kHz) produce a mechanical effect involving cavitation [28, 102] and microstreaming [6].

HIFUS may yield a significant thermal effect that may denature proteins [14, 102] and a mechanical effect capable of destroying tissues [11, 14]. Its thermal effect may elevate tissue temperature 20-30 ºC above body temperature [102] reaching up to 59-60 ºC [14, 28]; secondarily, it may activate non-thermal effects [14].

The mechanical effect of HIFUS may involve intramembrane cavitation [14]. However, the effect of these mechanisms is unpredictable to some extent, so its safety may be taken into account and requires accurate mathematical modeling to be applied [14]. However, this has not precluded its application for human diseases. HIFUS has been used for the ablation of malignant or dysfunctional tissues in the brain and other organs; it has been used in a wide variety of disor-

ders, from the destruction of kidney stones to lesioning overactive brain regions in neurological disorders [14].

It may seem like the HIFUS effect is restricted to destroying tissues, but it might be more complex. Brain ablation is not considered as a conventional neuromodulation technique. Still, some studies suggest that its primary destructive effect may activate some mechanisms of reversible neuromodulation [14] to adapt or compensate for the eliminated tissue.

However, HIFUS ablation may not be applied to every part of the brain. An important limitation of HIFUS is that some transducers can efficiently deliver ultrasound energy only close to the center of the brain [82], so some brain regions cannot be correctly focused [11]. This limitation might be reduced with future technical developments [82], which eventually may be available for their clinical use.

In summary, HIFUS ablation is relevant for several psychiatric and neurological disorders [14], including NP. Both clinical and experimental studies have tested its effects.

3.4. Therapeutic Potential of Ultrasound for Pain Neuromodulation

3.4.1. Low-intensity Focused Ultrasound

An increasing body of evidence indicates that FUS exerts a neuromodulatory effect on both central and peripheral nervous systems. Its mechanism of action may involve modulation of ion channels, an anti-inflammatory effect, neuroprotection, and remyelination. Those characteristics make FUS a right candidate for NP control. Several studies from preclinical models to controlled clinical trials have tested its therapeutic potential.

3.4.1.1. Experimental Models

LIFUS (14-93 W/cm^2) has been used to modulate rat vagus and sciatic nerves [15, 103], among others, showing promising results to control NP. Damage to the common peroneal nerve causes NP responsive to mechanical stimuli, and this may be reduced by FUS even 48 h after a single application to the DRG [104].

LIFUS (1.0 W/cm^2) reduces mechanical allodynia after intercostal nerve damage in rats [105]. This intervention is accompanied by a regional subcutaneous temperature increase of 2.4 ºC that lasts for three minutes after treatment cessation [105]. In this model, LIFUS also reduced TNFα levels after nerve damage [105], suggesting that its beneficial effect involves an anti-inflammatory mechanism.

Further studies support the role of inflammation in NP and the beneficial effect of LIFUS. LIFUS (1.0 W/cm^2) reduces thermal hyperalgesia and mechanical allodynia after sciatic nerve damage [10, 106, 107]. This effect involves reducing substance P, (proinflammatory) TNF-α and interleukin 6 levels, while increasing (anti-inflammatory) interleukin 10 levels in the sciatic nerve [10, 106] and spinal cord [107].

LIFUS (300-400 mW/ cm^2) reduces thermal hyperalgesia after chronic constriction injury on the infraorbital nerve in rats [108]; this result is observed after a single LIFUS application, yields its maximal effect 24 h after treatment and lasts up to 48 h [108]. Some studies suggest that stimulation of the opioidergic signaling may be partially involved in the hypoalgesic effect of LIFUS [108].

After peripheral nerve damage in rats, the affected limbs are more sensitive to FUS than non-affected ones [109, 110], allowing a more selective treatment. It remains to be determined if this effect is related to a sensitization of the damaged nerve to the mechanical effect of FUS; however, it should be noted that this ability to discriminate an affected tissue might have diagnostic implications.

Some minor side-effects may occur with this therapy. Pulsed LIFUS (2.05 W/cm^2) applied to the dorsal root ganglion reduces vincristine-induced NP and hyperalgesia [111], but this effect is accompanied by transient edema (<48h) [111].

3.4.1.2. Clinical Studies

Most LIFUS studies are experimental models, and clinical trials are scarce [16]. In humans, ultrasound has been used in physiotherapy to reduce pain after trauma due to its thermal effect [16]. LIFUS is not recommended in all diseases due to a limited efficacy to reduce pain in some of them [112]. Despite those limitations, several attempts to control pain using ultrasound have been reported.

Some studies have shown that the human cerebral cortex is a therapeutic target for the neuromodulatory control of pain. Magnetic neuromodulation of the contralateral motor cortex yields a sustained relief in patients with NP [1]. In contrast, LIFUS stimulation of the primary somatosensory cortex (3 W/cm^2) elicits painful sensations in hands or fingers in human volunteers [15].

Thalamic LIFUS stimulation (14.5 W/cm^2 I_{SPPA}) reduces cortical brain activity as measured by electroencephalography, reducing the performance of healthy volunteers in a tactile discrimination task [27]; it remains to be determined if this effect could alter nociception. However, this study used a single-element FUS instead of a transducer array, increasing the possibility of modulating non-targeted regions along the ultrasound beam [27].

Regarding the peripheral nervous system, preliminary studies show that non-focused ultrasound techniques (such as image-guided point-of-care ultrasound) reduce inflammation and pain in patients with peripheral nerve compression syndromes improving quality of life measures [113].

Clinical trials have shown that a 40-min FUS application increases mood and reduces pain in human patients [16, 114] in a crossover placebo-controlled clinical trial. Beyond its therapeutic effect, LIFUS may also be used for brain mapping since a selected region may be stimulated or inhibited by FUS, while a physician observes its impact on clinical manifestations [17]. Once a region shows a central role in presenting a disease or a specific symptom, it might be selected for LIFUS neuromodulation or permanent ablation using HIFUS.

Few studies are testing its effect on conditions like post-amputation pain or fibromyalgia. Anecdotic case-reports suggest that ultrasound reduces pain due to neuromas but not phantom pain after amputation [115]. Combined application

Table 2. LIFUS intensities leading to analgesic effects in experimental models.

Experimental Model	FUS Intensity (Range, W/cm^2)	Refs.
Mechanical allodynia after intercostal or sciatic nerve damage	1.0	[10, 105-107]
Thermal hyperalgesia after sciatic or infraorbital nerve damage	1.0-400	[10, 106-108]
Vincristine-induced NP	2.05	[111]

Table 3. Characteristics of clinical trials showing an analgesic effect of LIFUS.

Medical Condition	FUS Intensity (W/cm^2)	Type of Study	Total Number of Patients (Gender)	Outcomes	Refs.
Fibromyalgia	1.5, combined with connective tissue manipulation and high-voltage pulsed galvanic stimulation	Observational prospective cohort study	20 (20 female)	Reduced VAS score	[116]
Fibromyalgia	0.5, combined with inferential current	Randomized, single-blind, controlled trial	17 (17 female)	Reduced VAS score	[117]
Fibromyalgia	2.5, combined with inferential current	Randomized trial (no sham or placebo groups)	50 (50 female)	Reduced VAS score	[118]
Lumbar spinal stenosis	1.5, combined with physical exercise	Randomized controlled trial	45 (32 female, 13 male)	Reduced VAS score	[119]
Chronic nonspecific low back pain	1.0, combined with physical exercise and laser therapy	Randomized controlled trial	45 (13 female, 32 male)	Reduced VAS score	[122]
Lumbar radiculopathy	1.3, combined with transcutaneous electric stimulation	Randomized, single-blind (no sham or placebo group)	54 (36 female, 18 male)	Reduced VAS score	[121]
Cervical radiculopathy	1.5	Controlled, single-blind trial	29 (20 female, 9 male)	Reduced VAS score	[123]
Osteoarthritis	1.0, combined with transcutaneous electrical stimulation and heat application	Open-label uncontrolled trial	37 (27 female, 10 male)	Reduced VAS score	[126]

of connective tissue manipulation, high-voltage pulsed galvanic stimulation, and ultrasound (1.5 W/cm^2) to patients with fibromyalgia leads to a 45% reduction in pain intensity and other symptoms that remains one year after treatment in 21% of them [116]. In other studies, a combination of electric current application and ultrasound (0.5-2.5 W/cm^2) has been effective in improving pain and sleep disturbances in this population [117, 118].

Regarding chronic low back pain, the combined application of physical exercise and ultrasound (1.5 W/cm^2) reduces pain and analgesic use in patients with lumbar stenosis [119]. Depending on its parameters, its mechanism of action may involve ablation of the lumbar medial branch nerve, as observed in experimental models [120]. Some single-blind clinical studies suggest that the combination of transcutaneous electric stimulation and ultrasound (1.3 W/cm^2) might reduce pain in patients with chronic lumbar radiculopathy [121]. However, ultrasound (1 W/cm^2) may be effective by itself for non-specific low-back pain [122]. This treatment may also be combined with laser therapy [121]. However, ultrasound (1.5 W/cm^2) is not only applicable in the lumbar region since it also reduces pain in cervical radiculopathy [123].

FUS might be useful in rheumatic diseases. Pain management in these diseases is complex since it involves both inflammatory and neuropathic mechanisms, as well as central sensitization [124]. Therapeutic ultrasound reduces pain in patients with osteoarthritis according to an anecdotic trial, but ultrasound intensity was not reported, and no control group was included [125]. Ultrasound (1 W/cm^2) is also analgesic in this disease when combined with transcutaneous electrical stimulation and heat application [126].

In summary, despite plenty of experimental models showing a beneficial effect of LIFUS for NP after peripheral nerve damage, clinical trials in human patients are scarce; however, those studies are consistent with the therapeutic potential of LIFUS to control NP caused by chronic nerve compression. Further studies are needed to evaluate the effect of LIFUS in other disorders presenting with NP.

3.4.2. High-intensity Focused Ultrasound

3.4.2.1. Experimental Models

In contrast to LIFUS, HIFUS has been predominantly tested in the clinical setting, and barely in preclinical studies, but some experimental evidence has been reported. HIFUS

(1,850-3,160 W/cm^2) generates a reversible and partial conduction block in damaged nerves in a rat model of diabetic neuropathy [127-129], possibly reducing NP. Still, its potential side-effects were not evaluated in those studies except for the disruption of the myelin sheath [128] without apparent nerve degeneration [129].

3.4.2.2. Clinical Studies

Some authors have suggested the use of HIFUS for NP control [11, 130], and it has been tested in human patients [82, 131]. Neurosurgical interventions for NP have been directed to the cerebral cortex, the cingulum, the thalamus, the spinal cord, and peripheral nerves [132]. Still, to the best of our knowledge, human HIFUS studies for this disorder are only a few. In those cases, FUS may comply with two strategies: to ablate brain regions and to modulate cerebral vessel permeability [82].

Thalamic HIFUS ablation has been tested to reduce NP from several medical conditions, such as post-herpetic neuralgia, lumbar nerve root compression, brain lesions, spinal cord injury, and peripheral nerve damage [11]. This treatment showed promising results in some cases, most of them stopping analgesic use one year after treatment [70, 133].

Ablation of the central lateral nucleus of the thalamus shows a 49% improvement in pain scores three months after surgery that gets close to 60% at 1-year follow-up according to a large case-series [11, 18, 133]. Its main complication is intracranial hemorrhage, which resolves after 24 h but may yield some subtle sequelae still observable one year after treatment [6, 70].

HIFUS may be beneficial to control pain from several etiologies. In cancer-related pain, HIFUS may be effective through several mechanisms: on the one hand, HIFUS ablation may reduce pain by decreasing tumor mass [6]; on the other hand, increased tissue temperature may cause local denervation of nociceptive terminals [6, 70]. It has been reported that the palliative effect of HIFUS in cancer-related pain is not dependent on tumor control [6], suggesting that its mechanism of action goes beyond tissue ablation and may include neuromodulatory mechanisms.

In those patients, HIFUS may be helpful to control tumor growth, to stimulate the immune response against the tumor, and to enhance the effect of chemotherapy and radiotherapy [6]. For those reasons, MRI-guided HIFUS has been approved by the Food and Drug Administration to reduce pain in patients with bone metastases [6]. Some placebo-controlled clinical trials have shown that this treatment is effective in 60-100% of the patients with bone metastases and may completely abolish pain in about 20% of them [6]; in most of the patients, this beneficial effect may be observed three days after treatment and may last for three months [6].

Paradoxically, 32% of the patients may experience pain during treatment [6]; little or no pain may occur in 48.3% of patients, moderate pain in 14%, and brief but intense pain in 37.6% [131]. This pain may last for two days [131]. It should be noted that cancer-related pain and NP have different pathophysiological mechanisms, but, as discussed in the previous sections, both forms of pain may coexist and might be closely related to each other.

HIFUS has also been used in pancreatic cancer, showing pain relief in 81-86% of the patients [6, 70]; some studies suggest that its effect may last for 17 months [6]. In these patients, side-effects from HIFUS might be abdominal pain, edema, or skin burns in up to 5.9% of the cases; bowel perforation, the most severe complication, is extremely rare (0.3%) [6]. Finally, in these cases, ultrasound-guided HIFUS is preferred over its MRI-guided counterpart since it may be better adjusted for a breathing-induced displacement of the pancreas during its application [6]. However, this limitation may be reduced using general anesthesia with controlled respiration during the procedure [6].

According to some case-series or case-reports, HIFUS has also been used to reduce pain in other cancer types such as hepatocellular and cervical carcinomas, renal malignancies, and lymph node metastases, showing similar results [6].

Finally, HIFUS yields a 60% reduction in low back pain secondary to facet joint arthropathy (zygapophyseal joint arthropathy) that is observable six months after treatment as reported in a case series [70]. HIFUS reduces pain on walking in patients with osteoarthritis of the knee joint in another case-series [70]. Half of the patients still show reduced pain six months after treatment [70].

In summary, clinical trials show that HIFUS is effective in reducing NP in several disorders, although only a few studies have been reported. It is also beneficial for cancer-related pain, which may be neuropathic in some cases. Moreover, its application may be extended to other diseases, including chronic pain in musculoskeletal disorders.

CONCLUSION

An increasing body of evidence describes FUS mechanism of action; it may involve both thermal and non-thermal (mechanical) effects modulating ion channels, glutamatergic neurotransmission, cerebral blood flow, inflammation and neurotoxicity, neuronal morphology and survival, nerve regeneration and remyelination. An auditory component may occur in some cases. Its effect may be long-lasting, either excitatory or inhibitory, and is reversible unless tissue ablation occurs. Those mechanisms are relevant for NP since its underlying damage may involve inflammation, demyelination, and cell death. NP may also participate in some cases of tumoral compression or infiltration of nerve structures or chemotherapy-induced neurotoxicity.

Experimental models have shown that LIFUS may reduce allodynia, suggestive of NP, after peripheral nerve damage, possibly through an anti-inflammatory mechanism. To the best of our knowledge, HIFUS has not been tested in those models. Few clinical studies support the beneficial effect of LIFUS to reduce pain in nerve compression syndromes, but HIFUS has been more extensively studied. Thalamic HIFUS ablation reduces NP from several etiologies showing a 49-60% efficacy [11, 18, 133]. Minor side-effects occur, but some subtle neurological sequelae are still observable one year after treatment [6, 70].

HIFUS ablation is also effective in reducing cancer-related pain, which may be NP. However, HIFUS is also effective in cancer patients when this pain is not neuropathic.

In these patients, the effect of HIFUS is not dependent on tumor control, suggesting that its mechanism of action may be neuromodulatory. For those reasons, MRI-guided HIFUS has been approved by the Food and Drug Administration to reduce pain in patients with bone metastases [6]. HIFUS may also reduce pain in musculoskeletal disorders. However, clinical studies testing FUS does not always include sham or placebo groups, limiting their interpretation.

This narrative review shows that an increasing body of evidence supports the therapeutic potential of both LIFUS and HIFUS for either central or peripheral NP with clinical efficacy and minor side-effects, improving patients' neurological condition and quality of life. More randomized placebo-controlled clinical trials are needed to determine the therapeutic potential of FUS to control NP in medical practice. Despite the progress in pain research, the management of NP is challenging. Although numerous treatment options are available for relieving NP, there is no consensus on the most appropriate treatment.

LIST OF ABBREVIATIONS

BBB	=	Blood-Brain Barrier
BOLD	=	Blood Oxygen Level-Dependent
CNS	=	Central Nervous System
DRG	=	Dorsal Root Ganglion
FUS	=	Focused Ultrasound
HIFUS	=	High-Intensity FUS
I_{SPPA}	=	Spatial-Peak Pulse-Average Intensity
I_{SPTA}	=	Spatial Peak Temporal Average Intensity
LIFUS	=	Low-Intensity FUS
MRI	=	Magnetic Resonance Imaging
NP	=	Neuropathic Pain
TMS	=	Transcranial Magnetic Stimulation
TNFα	=	Tumor Necrosis Factor α

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