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Brain-Focused Ultrasound Therapy: Current Applications and Future Prospects

Felipe Velasquez Botero[1], Maria Alejandra Nieto Salazar[2], Guillermo Andres Moreno Cortes[3], Miguel Eduardo Rodriguez Rodriguez[4], Jessica Mariela Amaya Alvarez[5], Valentina Joshay Contreras Duran[6], Inés Yaritza Cury Perea[7], Jose Clemente Noriega Valdez[8], Ericka Alexandra Saldana[9], Karla Banuelos Gonzalez[10], Osman Adalberto Alvarado Portillo[11], Gioacchino Di Marco Stefano De Sario Velasquez[12], Arnold Ocoro Vallecilla[13] and Adriana Carolina Toro Velandia[2]

[1]*CES University, Colombia. Larkin Community Hospital, Miami, Florida, USA*

[2]*Juan N. Corpas University, Colombia. Larkin Community Hospital, Miami, Florida, USA*

[3]*Department of Family Medicine, FUCS University, Colombia. Larkin Community Hospital, Miami, Florida, USA*

[4]*Universidad de Oriente, Venezuela. Larkin Community Hospital, Miami, Florida, USA*

[5]*Universidad Salvadoreña Alberto Masferrer, El Salvador. Larkin Community Hospital, Miami, Florida, USA*

[6]*University of Los Andes, Venezuela*

[7]*Universidad de Manizales, Colombia*

[8]*Autonomous University of Baja California, Mexico*

[9]*CBCS, El Salvador*

[10]*Centro de Estudios Universitarios Xochicalco, Mexico*

[11]*Universidad de El Salvador, El Salvador*

[12]*Universidad De Oriente, Venezuela*

[13]*Universidad Santiago de Cali, Colombia*

[14]*Juan N. Corpas University, Colombia. Larkin Community Hospital, Miami, Florida, USA*

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***Corresponding author:** Felipe Velasquez Botero, CES University, Colombia. Larkin Community Hospital, Miami, Florida, USA. Maria Alejandra Nieto Salazar, Juan N. Corpas University, Colombia. Larkin Community Hospital, Miami, Florida, USA.

Abstract

Interventional therapies to address brain disorders carry out an additional risk due to the central nervous system's difficult access and intrinsic complexity. Focused ultrasound therapy (FUT) is an incision-free, minimally invasive procedure that employs sound waves to produce either thermal ablation or neuromodulation according to the waveform intensity. Despite the growing evidence of the benefits and advantages of FUT, many of its potential applications have not been explored in their entirety. The mechanism of action of Focused Ultrasound involves the generation of mechanical and thermal effects on the target tissue. Magnetic resonance-guided is the most common method for delivery of FUT in the brain. Most benefits of brain FUT can be attributed to its ability to ablate target tissue or modulate neuronal activity. However, this technology can also be used to open, temporarily and reversibly, the blood-brain barrier to allow the delivery of medications directly to the affected tissue. Currently, there are few FDA-approved brain FUT applications, including the treatment of essential tremor, Parkinson's disease tremor, and other kinetic disorders. However, several other therapeutic applications are in the early stages of research, such as epilepsy, trigeminal neuralgia, obsessive-compulsive disorder, depression, and utilizing FUT for the local delivery of drugs. This review aims to highlight some of the most significant present and future applications of focused ultrasound therapy in neurological conditions. Considering its apparent safety profile and efficacy, this emerging technology could become a feasible therapeutic alternative for multiple nervous system disorders.

Keywords: Focused Ultrasound; Brain Focused Ultrasound Therapy; Ultrasound Therapy Neurological Disease; Central Nervous System

Abbreviations: FUT: Focused Ultrasound Therapy; FUS: Focused Ultrasound; US: Ultrasound; ET: Essential Tremor; VIM: Ventral Intermediate Nucleus; FDA: Food and Drug Administration; RFA: Radiofrequency Ablation; DBS: Deep Brain Stimulation; PD: Parkinson's Disease; BBB: Blood-Brain Barrier; IASP: International Association for the Study of Pain; TCAs: Tricyclic Antidepressants; SNRIs: Selective Serotonin-Norepinephrine Reuptake Inhibitors; LILFUS: Low-Intensity Low-Frequency Ultrasound; HIFU: High-Intensity Focused Ultrasounds; TN: Trigeminal Neuralgia; MR-HIFU: Magnetic Resonance Imaging-Guided High-Intensity Focused Ultrasound (MR-HIFU); AEDs: Antiepileptic Drugs; SRS: Stereotactic Radiosurgery; DRE: Drug-Resistant Epilepsy; MRI: Magnetic Resonance Imaging; VNS: Vagus Nerve Stimulation; RNS: Responsive Neurostimulation; OCD: Obsessive-Compulsive Disorder; MDD: Major depressive disorder; CNS: Central Nervous System; MRgFUS: Magnetic Resonance Guided Focused Ultrasound; AD: Alzheimer's Disease; MB: Microbubbles, PNP: Peak Negative Pressure (PNP)

Introduction

Focused ultrasound therapy (FUT) is an incision-free, minimally invasive procedure that uses sound waves to address various medical conditions. In response to the sound waves, tiny patches of tissue in the body are heated up and ablated or altered without disrupting surrounding structures. It combines different acoustic energy frequencies to provide its therapeutic effect [1]. FUT can be applied to different conditions: movement disorders (tremor), uterine fibroids, and cancer (prostate, breast, liver, kidney, pancreas, bone, and brain) [1,2]. By precisely converging an ultrasound beam on a specific target inside the body, focused ultrasound delivers energy into a tiny focal spot inside the body. The use of high-intensity FUT may result in coagulation necrosis in biological tissues. In contrast, low-intensity FUT leads to non-destructive heating of the tissue [3].

FUT involves two main mechanisms: thermal effects through ultrasound (US) absorption and mechanical effects through acoustic cavitation. Thermal effects are caused by the absorption of acoustic energy and the conversion of that energy into heat at the targeted location. The heat increases the temperature rapidly to 60°C or higher, causing local protein denaturation and coagulative necrosis. As thermal effects of US absorption are linearly proportional to the sonic intensity, they can be predictable. In contrast to thermal ablation, mechanical ablation cause less damage to the surrounding tissue since there is no heat perfusion via blood flow, and the treated area coincides with the ultrasound focussed region. With this technique, there is no coagulation necrosis. Mechanical acoustic cavitation is caused by the interaction between ultrasound waves and gas bubbles. In the tissue, at a high acoustic pressure level, the peak positive part of the sinusoidal wave travels faster than the peak negative part of the wave due to the non-linear ultrasound wave propagation, which creates a shockwave as the ultrasound wave penetrates the tissue. The cavitation phenomenon occurs when ultrasound wave intensity exceeds a specific threshold, as the negative pressure is sufficiently high to overcome the surface tension of the gas nuclei available in the tissue [3].

FUT has recently been extensively investigated for treating neurological conditions due to its minimally invasive nature, absence of radiation, relatively low cost, immediate effects, rapid recovery, and decreased risk of complications [4]. Moreover, this technique allows a real-time visualization of the brain's target cells, which is highly desirable in managing brain conditions. In this review, we provide an overview of current applications of focused ultrasound therapy in the brain, associated limitations, and potential uses in the future.

Movement Disorders

Essential Tremor

Tremors are involuntary rhythmic and oscillatory movements of a body part with a relatively constant frequency and variable amplitude. This is the most common type of movement disorder and includes a variety of conditions, of which Essential Tremor (ET) is the most common [5]. There is an estimated prevalence of up to 5% of the population worldwide, and family history can be identified in nearly 50% of cases [6]. The majority of patients with ET are older than 65 years of age, but it can affect individuals of any age [5]. The condition is characterized by a bilateral 6-to-12 Hz postural tremor of the hands, followed by a kinetic and resting component. Most often, upper limbs are affected, but as the disease progresses, the head and voice (less commonly, legs, jaw, face, and trunk) may also be affected. Despite its benign effect on life expectancy, it often causes embarrassment and, in a small percentage of cases, severe disability. In addition, it is common for the symptoms to progress over time, causing patients to change jobs or retire early [5]. When treating essential tremor, patients are often challenged with several medications if the first choice does not work or is associated with debilitating side effects. Typically, propranolol or primidone are used as the first line of treatment. Other options include gabapentin, pregabalin, topiramate, benzodiazepines, beta-blockers, nimodipine, and clozapine [5]. Unfortunately, some patients do not fully respond to drug therapy despite increasing their doses or combining different medications, consequently requiring invasive procedures such as radiofrequency ablation (RFA) or deep brain stimulation (DBS). In order to overcome this limitation, brain FUT has been proposed as an alternative treatment method [7]. Using this novel non-invasive therapeutic technology, patients with essential tremor can improve their quality of life and decrease their costs of care. As a result of directing multiple US beams accurately at targets deep within the brain, sound waves are capable of ablating the ET foci precisely. For this movement disorder, the primary area to target is the ventral intermediate nucleus (VIM) of the thalamus, as well as other adjacent tissues.

In 2016, the FDA approved the use of focussed ultrasound as a treatment alternative for essential tremor. Since then, current treatment protocols have been conducted on only one side of the brain, with actual studies examining its efficacy for bilateral treatment [7]. Compared to other non-pharmacological treatments (RFA and DBS), focused US is a non-invasive procedure that offers a reduced risk of treatment-related complications as it affects a lesser amount of the surrounding tissues [6,7]. Additionally, this technique allows patients to recover rapidly and resume normal activities within a short time. In light of the above, brain FUT has emerged as a potential alternative for treating patients with drug-resistant essential tremor and those with contraindications to invasive treatments.

Parkinson's Disease Tremor

Parkinson's disease (PD) is the second most common age-related neurodegenerative disorder in developed nations, following Alzheimer's disease. Approximately 1% of the population over the age of 60 is affected by the disease [8]. Typically, clinical

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manifestations include the presence of extremities rigidity, resting tremor, bradykinesia, and postural imbalance. Since there is no absolute cure for PD, therapeutic interventions focus on providing symptomatic relief, improving quality of life, and reducing complications associated with the disease. The most common treatment options for psychomotor dysfunction associated with Parkinson's disease include pharmacotherapy, deep brain stimulation, and physical therapy [9]. However, some patients do not experience complete symptomatic remission after receiving these treatments. Brain-focused US is a relatively new intervention modality that has shown to provide symptomatic relief by interrupting the circuits involved with tremors and dyskinesia on a deep level within the brain [10]. A clinical trial conducted in 2017 found that this therapy significantly improved symptoms from baseline by 62% [11]. FUT targets for the treatment of PD-related movement disorders include thalamic nuclei (for PD tremor), pallidothalamic tract (for PD tremor, akinesia, or dyskinesia), and globus pallidus or subthalamic nucleus (for PD dyskinesia). The second mechanism of action provided by FUT is the opening of the blood-brain barrier (BBB), a lining structure formed by tightly aligned cells in the brain circulation. The permeation of the BBB can allow medication and antibodies to diffuse into the brain, potentially preventing progression and/or restoring function [10]. Following brain FUT, patients often experience finger paresthesias (40%), ataxia (35%), and orofacial paresthesias (25%). In most cases, side effects are mild and self-limiting [11]. In 2018, brain-focused US was approved by the FDA for the treatment of PD-related tremor. The approval was further expanded to include other PD symptoms such as stiffness, dyskinesia, and slowness. In this context, brain FUT is primarily indicated for patients with medication-resistant symptoms [12]. Several other continents have also established the use of the FUT as a therapeutic measurement for PD tremor (Europe, Asia, Latin America). As a result, the use of this therapy continues to expand, and further research will lead to technical improvements to benefit patients suffering from psychomotor dysfunction.

Chronic Neuropathic Pain

According to the International Association for the Study of Pain (IASP), neuropathic pain is the presence of pain caused by a lesion or disease in the somatosensory nervous system, including the peripheral fibers (Aβ, Aδ, and C fibers) and central neurons [13,14]. Numerous causes of neuropathic pain have been identified, and its prevalence is predicted to increase as the world's population ages and diabetes mellitus prevalence increases [14]. Several conditions and pathophysiological states can lead to the development of neuropathic pain, including viral infections such as post-herpetic neuralgia, HIV, leprosy, chemotherapy-induced peripheral neuropathies, autoimmune diseases such as multiple sclerosis and Guillain-Barre syndrome, and nerve damage caused by trauma. [15]. Patients typically report specific symptoms, such as hyperalgesia, allodynia, and paresthesias. Pain caused by neuropathy often manifests spontaneously, without the need for stimulation. Most of the time, the symptoms persist and fail to respond to painkillers. Sleep problems, anxiety, and depression are common in patients with chronic neuropathic pain, and their quality of life is lower than that of patients with chronic non-neuropathic pain [14,15]. The Special Interest Group on Neuropathic Pain recommends first-line treatment for neuropathic pain, including gabapentinoids, tricyclic antidepressants (TCAs), or selective serotonin-norepinephrine reuptake inhibitors (SNRIs). Second-line and third-line alternatives include lidocaine, capsaicin, opioids (tramadol, oxycodone, and morphine), and botulinum toxin-A [13,14,15]. Notably, up to 70% of patients do not experience sufficient pain relief from pharmacotherapy alone. There is also a high potential for misuse and addiction with some of these medications [13,14].

The application of focused ultrasound for thalamotomy has been approved to treat both bone metastasis pain and persistent neuropathic pain [16]. Brain-focused ultrasound is a newly developed non-invasive therapy that uses high-energy ultrasound waves to accurately transcranially ablate a target volume under ultrasonographic guidance without causing harm to nearby healthy tissues. Compared with traditional non-invasive brain stimulation methods (magnetic or electric stimulation), FUS has a higher spatial resolution and may penetrate deeper into the brain. Since this technique allows it to target any peripheral or central nervous system region, it is an ideal tool for pain neuromodulation. In addition, brain FUT is capable of providing a wide range of stimulation parameters resulting in different biological effects, ranging from reversible facilitation or suppression of neural activity (by using low-intensity, low-frequency ultrasound, or LILFUS) to irreversible tissue ablation (by using high-intensity focused ultrasounds, or HIFU) [16,17].

Trigeminal Neuralgia

Trigeminal neuralgia (TN) is characterized by sudden, intense, brief pain episodes reminiscent of electric shocks. These stabbing and recurring pain episodes affect one or more trigeminal nerve branches: ophthalmic (V1), maxillary (V2), and mandibular (V3) [18,19,20]. People with this condition are severely disabled, resulting in a decrease in their quality of life on an everyday basis. According to epidemiological studies, these patients are at an increased risk for anxiety, depression, and suicide: which emphasizes the value of early diagnosis and effective treatment [19]. The incidence is higher in females than males (2-3:1) [20]. It is believed that TN is caused by a combination of factors resulting in neurovascular disturbance. These factors include peripheral diseases of the nerve root (compression or traction), brain stem disturbances, basal ganglia, and cortical pain modulatory processes. The primary treatment option for TN consists of mono- or combination therapy with anticonvulsants (carbamazepine and oxcarbazepine). A second-line option may include baclofen, topiramate, gabapentin, and pregabalin [20]. More invasive measures, such as nerve blocks or surgery, may

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be considered when patients present significant adverse effects or do not respond to pharmacological measures. The surgical management of TN (central lateral thalamotomy) involves an invasive disruption of the thalamocortical and corticocortical networks, which control sensory, cognitive, and emotional aspects of pain. Since the introduction of magnetic resonance imaging-guided high-intensity focused ultrasound (MR-HIFU), procedural-related morbidity for TN has significantly improved [21,22]. By targeting the ganglion root through the foramen ovale, MRgFUS offers the possibility of an effective non-invasive treatment for primary trigeminal neuralgia. While this procedure is technically and methodologically feasible, it may still have several limitations based on the large neurovascular structures surrounding the treatment area, the malfunctioning of the masseter muscle in some cases, and the concern about the type of anesthesia needed. Although MR-HIFU appears to be a promising technique for treating trigeminal neuralgia, further research and large-scale clinical trials are required to ensure its safety and efficacy [23].

Epilepsy

Epilepsy is a chronic neurological disorder characterized by aberrant neuronal hyperexcitability, usually attributed to an idiopathic cause [24,25]. The incidence ranges from 1 to 3% of the population. Typical symptoms include the presence of unprovoked, spontaneous, and recurrent seizures [26]. An electroencephalographic evaluation, in combination with its classic symptoms, provides a definitive diagnosis of epilepsy. Generally, standard antiepileptic drugs (AEDs) treatment provides adequate control of disease activity. However, it has been documented that up to 30% of patients may be resistant to drug therapy [24]. Some therapeutic alternatives for these patients include epilepsy surgery, thermal ablation, stereotactic radiosurgery (SRS), and deep brain stimulation [27]. However, several clinical and technical limitations are associated with these procedures, including their invasive nature, high costs, and low success rates [27]. To overcome these limitations, the use of brain-focused US for managing drug-resistant epilepsy (DRE) is currently being investigated [27,28]. In this emerging technology, US beams are projected non-invasively into epileptogenic foci without compromising surrounding normal brain tissue [25,27]. Depending on the energy intensity and frequency applied, these waves can produce two therapeutic effects: ablation and neuromodulation. High-energy sound waves (230-1000 kHz) with continuous application result in localized thermal ablation of the epileptic network [27]. This energy is directed to a central point at which the temperature can be increased or decreased, creating protein denaturation and coagulation necrosis on the target. Using MRI simultaneously, local effects of thermal coagulation can be monitored and controlled in real-time [27]. Although this therapy has shown encouraging results in trials of patients with brain tumors, neuropathic pain, and movement disorders, its use in epilepsy is hampered by technical difficulties (i.e., injury to normal tissue) [27,28]. Currently, these limitations are being addressed in small-scale clinical trials (NCT02804230).

The second effect of FUS is neuromodulation, which can be achieved by a pulsed application of low-intensity sound waves [24,25,27]. Historically, a variety of techniques have been used to modulate aberrant neuronal activity, including vagus nerve stimulation (VNS), deep brain stimulation (DBS), and responsive neurostimulation (RNS) [24,25,26]. It should be noted that these modalities are either invasive or have low specificity/spatial depth [25]. In contrast, brain FUS is a non-invasive approach that offers effective modulation of neuronal activity due to its high spatial specificity and depth of penetration [24,25]. Low-intensity pulsed US waves can be directed to the epileptic focus, causing a reduction in frequency and/or duration of seizures [25]. In animal models, Zhang et al. [25] found that brain network connections decreased significantly after applying low-intensity ultrasound pulses in epileptic mice [29]. Moreover, his group demonstrated that this therapy reduced seizure frequency and duration in a primate model of epilepsy [25]. These results suggest that low-intensity FUS therapy in humans could be capable of effectively reducing epileptic seizures and suppressing epileptiform activities. However, to our knowledge, there is no conclusive data regarding the effectiveness, feasibility, and safety profile of this procedure in humans [25,30]. Clinical trials are currently being conducted to provide further insight into this topic (NCT02151175).

Based on the above, brain FUS represents a promising novel technology that offers a non-invasive alternative to patients with drug-resistant epilepsy in order to improve their life quality while reducing the necessity for invasive procedures and their associated downsides.

Psychiatric Disorders: OCD & MDD

Obsessive-compulsive disorder (OCD) is a psychiatric condition manifested by the presence of repetitive thoughts. The disorder is characterized by intrusive and unwanted obsessions that lead to actions-compulsions in response to the anxiety they cause. The age of onset varies between 20 and 30 years, with men being more affected during their childhood years and women during adulthood. There is a high correlation between OCD and other disorders such as anxiety and depression [31]. Major depressive disorder (MDD) is defined as the presence of anhedonia and a depressed emotional state for at least two weeks, along with other symptoms, including sleep disturbance, loss of appetite, and suicidal thoughts. Women of all ages are most likely to suffer from MDD. Biological and psychological factors are involved in the etiology of depression, and it is believed that a decrease in certain neurotransmitters could explain most cases [31,32]. Pharmacological treatments in conjunction with cognitive-behavioral therapy have proved effective in reducing the symptoms of OCD and depression. However, a significant percentage of patients do not experience positive outcomes after undergoing these therapies. In cases where conventional treatment fails to provide adequate relief, patients may be

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candidates for neurosurgical intervention, including SRS, RFA, and brain-focused ultrasound [33,34,35,36]. Brain FUT offers more significant advantages compared to other interventional approaches since incisions and radiation are not required, reducing the risk of complications.

Furthermore, most side effects are mild and self-limited, including nausea, headaches, and transient paresthesias [37]. In a recent study by Chang et al. [37] 11 patients with refractory OCD and 4 patients with refractory depression underwent brain FUT demonstrating an adequate treatment response. During a follow-up period of 12 to 24 months, several disease-activity clinical scores improved by 50 - 83% [37]. Brain FUT has not yet been approved for use as a treatment for OCD or depression by any regulatory body in the world. However, further developments in medical science may open the possibility of optimizing the details of this technique so that it can be used as a non-invasive treatment for mental disorders.

Localized Drug Delivery Therapy

Anti-tumor Agents

In 2019, 1,752,735 new cancer cases were reported in the United States and 599,589 cancer-related deaths [38]. Brain and other nervous system cancer is the 10th leading cause of death for men and women, and it is estimated that 18,280 adults in the country will die from primary brain cancer and CNS tumors in 2022 [39]. Anti-tumor or antineoplastic agents are active forces or substances capable of halting or slowing the growth of tumors. These agents are often used to treat cancer [40]. They are categorized as alkylating agents, antimetabolites, natural products, hormones, antagonists, and miscellaneous. They can also be classified by indication, mechanism of action, chemical structure, or as cytotoxic or nonspecific vs. noncytotoxic or targeted. Almost all antineoplastic agents can cause hepatotoxicity, most likely due to intrinsic toxicity. Transaminitis and hyperbilirubinemia are typical manifestations during antineoplastic therapy. However, it is reversible by either ceasing or modifying treatment. This type of hepatotoxicity is dose-related and generally self-limited but can be severe [41].

Transcranial-focused ultrasound (FUS) is a non-invasive way to safely transmit acoustic energy with high accuracy. It can generate cytotoxicity within the tumor tissue via thermal ablation, radiosensitization, and sonodynamic therapy. FUS has the ability to open the BBB and improve the distribution of the drug through the extracellular space of the brain without causing any damage to the healthy tissue. Moreover, FUS is able to modulate the tumor microenvironment to generate an immune response. In recent years, MR-guided focused ultrasound devices have been modified to deliver focused energy in the human brain non-invasively, offering new treatment options for brain tumors (e.g., enhancing drug delivery directly to the tumor). To reach their targets within a brain cancer cell, systemic therapeutic agents must overcome numerous obstacles, including the BBB and the brain-tumor penetration barrier, which FUS can overcome. MRgFUS, in combination with microbubbles, has been used in preclinical models to strengthen the delivery of some agents that are too large to cross the BBB [42]. MRgFUS has also repeatedly opened the BBB in a rat glioma model. In this model, three weekly sessions of ultrasound-induced BBB disruption increased the concentration in the brain of IV-delivered liposomal doxorubicin, resulting in longer median survival times [43]. Additionally, the safety of these treatments has been investigated in primates [44]. The BBB was opened at 163/185 targeted locations within the visual field, and 24/25 FUS treatments successfully opened the BBB within the basal ganglia. There was no evidence of long-term visual or motor impairment in these primates [44]. As this technology continues to advance, it is anticipated that FUS will become a valuable asset in treating brain cancer, improving the quality of life of patients and their life expectancy.

Alzheimer's Disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder with widespread extracellular beta-amyloid plaques and intracellular neurofibrillary tangles primarily composed of hyperphosphorylated tau protein. These alterations lead to progressive nerve cell death and gliosis [45,46]. In the United States, AD is the sixth leading cause of death and a significant cause of disability. Additionally, AD is the most common cause of dementia in individuals above 65 years of age [46]. While the presentation of AD is varied, some symptoms may present at an early stage or preclinically, such as heightened anxiety, sleep changes, withdrawal, and depressive symptoms. Later, the symptoms may progress to confusion, disorientation, impaired judgment, and behavioral changes [46]. The current treatment options for Alzheimer's disease (AD) are primarily used to manage cognitive symptoms rather than address progressive neurodegeneration. The available medications include N-methyl-D-aspartate receptor antagonists (memantine) and cholinesterase inhibitors (donepezil, galantamine, rivastigmine) [45]. While many of the current treatment options for Alzheimer's disease have remained unchanged for a long time, magnetic resonance-guided focused ultrasound (MRgFUS) has been demonstrated to be a valuable non-invasive method for treating the disease. This technology could play an essential role in the treatment of Alzheimer's disease due to its ability to reversibly open the BBB, which has been shown to reduce amyloid-beta plaque buildup [47]. The reversible opening of the BBB has been demonstrated in preclinical trials to improve memory and cognitive function by stimulating neurogenesis and neuromodulation. Moreover, using FUS in conjunction with microbubble-guided drug infusion has improved cognition via increased cholinergic function and neuron development [48]. However, conclusive data on established parameters and standards regarding the novel therapeutic application of FUS is yet to be determined. Nonetheless, ongoing

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studies have determined FUS to be well tolerated among patients and have not reported adverse effects or neurological complications post-treatment [47].

Gene Therapy

Gene therapy is a therapeutic technique used to correct disease in tissues by inserting or replacing defective genes with a functional copy of the gene [49]. This therapy can potentially improve many symptoms of the neurodegenerative disease while also correcting the pathogenesis via mechanisms of neuroprotection and neuroregeneration [50]. However, the utility and scope of application of gene therapy in organs, such as the brain, are limited by its accessibility to the affected area [51]. The brain is a complicated organ to access due to the physiology that separates blood from the brain and systemic circulation through the BBB. While viral vectors and intracerebral injections have been studied in attempts to utilize gene therapy targeting the CNS, these approaches have not been achieved to target specific areas of the brain efficiently. However, the integration of FUS and microbubble-mediated delivery has facilitated gene therapies to be administered systemically while achieving adequate penetrance of the BBB [52]. Although the integration of brain FUS with microbubbles (MB) has not been demonstrated to have many short-term or long-term adverse effects such as hemorrhage and inflammation, there are still many limitations on the knowledge for regionally directed therapy. For example, there is still a limited amount of information available regarding the transfection of different types of brain cells. Currently, research is being conducted to identify factors that might contribute to the transfection of cells, such as the type of vector used for gene delivery and the effect of FUS's peak-negative pressure (PNP) parameter [53].

Conclusion

Many current treatments for neurological diseases include strategies that are ineffective for a significant percentage of patients. For these individuals, it is imperative to perform procedures to eradicate the neurological problem's triggering focus. Despite their apparent efficacy, most of these procedures are invasive and may be associated with various complications or long-term sequelae. Brain-focused ultrasound therapy is an emerging technology that has shown considerable benefits in patients with different neurological conditions. Its non-invasive nature and ability to target neurological conditions without affecting normal brain tissue make it a valuable tool for treating brain diseases.

For individuals with movement disorders (ET and PD tremor) who have persistent symptoms despite taking multiple medications, brain FUT has been approved by the FDA as an effective therapeutic alternative. Similarly, this modality has been approved and adopted in several US institutions to treat chronic neuropathic pain. This represents a significant advance for managing these patients since they are often difficult to treat, and the medications commonly prescribed are prone to misuse or addiction. Further research is required to determine whether FUT can be used in specific conditions such as trigeminal neuralgia since this disease's complex anatomical and pathological structure makes the correct implementation of this treatment more challenging. In disorders such as epilepsy, various studies using brain FUT have demonstrated a high degree of efficacy due to its ability to provide both thermal ablation and neuromodulation of epileptic networks. Currently, human clinical trials are being conducted in order to determine whether this procedure is safe. In patients with psychiatric disorders, various preclinical studies have shown inconclusive results due to the multifactorial nature of these conditions, and further research is needed to establish the utility of this technique. Using FUT to generate transient openings in the BBB in animal models has shown great promise for generating localized drug delivery. Using FUT, different drugs can be delivered into the extravascular space and exert their effect directly on the affected tissue without harming healthy tissue. This could be extremely valuable for treating conditions such as brain cancer, Alzheimer's disease, and genetic disorders.

As a novel therapeutic modality, much remains to be learned about focused ultrasound therapy's potential application in the CNS. Despite this, the current approval of this technology for some difficult-to-treat neurological disorders, as well as ongoing research into its use and efficacy in various conditions, make it a promising therapeutic tool. With this review, we are confident to conclude that, as ultrasonographic technology advances, brain FUT would become a suitable method for routine clinical practice as it offers a non-invasive, low-cost, and safe therapeutic method, which is highly desired in any neurological disorder..

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