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LOW-INTENSITY FOCUSED ULTRASOUND FOR DRUG-RESISTANT EPILEPSY: NETWORK TARGETING, ACOUSTIC DOSE CONTROL, AND REVERSIBLE NONINVASIVE NEUROMODULATION

Abstract

Background. Drug-resistant epilepsy remains associated with recurrent seizures, injuries, cognitive decline, psychosocial disability, and premature mortality. Resective surgery and implantable neurostimulation can be effective, but many patients have bilateral, deep, multifocal, eloquent-cortex, or poorly localized epileptogenic networks that limit invasive treatment. Low-intensity focused ultrasound offers nonthermal, incisionless, millimeter-scale modulation of cortical and subcortical circuits.

Materials and methods. A structured narrative review integrated prospective trials, pilot studies, preclinical experiments, technical investigations, safety consensus statements, and registered protocols available through July 2026. Evidence was organized by mechanism, acoustic dose, skull transmission, target selection, electrophysiological engagement, clinical efficacy, safety, reproducibility, and implementation. A prospective multicenter, randomized, double-blind, sham-controlled study is proposed for adults with drug-resistant focal epilepsy unsuitable for curative resection.

Results. Human pilot studies show that sonication can be delivered to seizure-onset tissue without radiographic injury and can alter intracranial electroencephalographic activity, but seizure outcomes remain preliminary and heterogeneous. Therapeutic direction depends on carrier frequency, pulse duration, pulse-repetition frequency, duty cycle, pressure, exposure duration, target geometry, and brain state. The proposed primary endpoint is the proportion of participants achieving at least fifty-percent reduction in disabling-seizure frequency during months four through six without treatment-related neurological deterioration. Secondary endpoints include seizure freedom, electrographic burden, cognition, mood, quality of life, target-engagement biomarkers, skull-adjusted acoustic exposure, adverse events, and durability.

Conclusion. Low-intensity focused ultrasound is an investigational network neuromodulation strategy rather than an established epilepsy treatment. Clinical translation requires individualized acoustic modeling, sham control, mechanistic biomarkers, standardized safety reporting, and independent multicenter validation before routine adoption.

Keywords: drug-resistant epilepsy, low-intensity focused ultrasound, transcranial ultrasound stimulation, neuromodulation, epileptogenic network, acoustic modeling, seizure-onset zone, stereo-electroencephalography.

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НИЗКОИНТЕНСИВНЫЙ ФОКУСИРОВАННЫЙ УЛЬТРАЗВУК ПРИ ФАРМАКОРЕЗИСТЕНТНОЙ ЭПИЛЕПСИИ: СЕТЕВОЕ ТАРГЕТИРОВАНИЕ, КОНТРОЛЬ АКУСТИЧЕСКОЙ ДОЗЫ И ОБРАТИМАЯ НЕИНВАЗИВНАЯ НЕЙРОМОДУЛЯЦИЯ

Аннотация

Актуальность. Фармакорезистентная эпилепсия остается связанной с повторными приступами, травмами, когнитивным снижением, психосоциальной дезадаптацией и преждевременной смертностью. Резективная хирургия и имплантируемая нейростимуляция могут быть эффективными, однако у многих пациентов выявляются двусторонние, глубокие, мультифокальные, расположенные в функционально значимой коре или недостаточно локализованные эпилептогенные сети, ограничивающие инвазивное лечение. Низкоинтенсивный фокусированный ультразвук обеспечивает нетермическую, безразрезную и высокоточную модуляцию корковых и подкорковых структур.

Материалы и методы. Структурированный нарративный обзор объединил проспективные исследования, пилотные испытания, доклинические эксперименты, технические работы, консенсусные рекомендации по безопасности и зарегистрированные протоколы, доступные до июля 2026 года. Доказательства систематизированы по механизму, акустической дозе, прохождению через череп, выбору мишени, электрофизиологическому вовлечению, клинической эффективности, безопасности, воспроизводимости и внедрению. Предложено проспективное многоцентровое рандомизированное двойное слепое плацебо-контролируемое исследование взрослых с фармакорезистентной фокальной эпилепсией, которым не показана радикальная резекция.

Результаты. Пилотные исследования у человека показывают, что соникация может доставляться к зоне начала приступа без радиологически выявляемого повреждения и изменять интракраниальную электроэнцефалографическую активность, однако противосудорожные результаты остаются предварительными и неоднородными. Направленность эффекта зависит от несущей частоты, длительности импульса, частоты повторения, рабочего цикла, давления, продолжительности воздействия, геометрии мишени и функционального состояния мозга. Первичная конечная точка - доля пациентов со снижением частоты инвалидизирующих приступов минимум на пятьдесят процентов в течение четвертого–шестого месяцев без связанного с лечением неврологического ухудшения. Вторичные показатели включают свободу от приступов, электрофизиологическую нагрузку, когнитивные функции, настроение, качество жизни, биомаркеры вовлечения мишени, акустическую экспозицию, нежелательные явления и устойчивость эффекта.

Заключение. Метод остается экспериментальной сетевой нейромодуляцией, требующей индивидуального акустического моделирования, имитационного контроля, механистических биомаркеров, стандартизированной отчетности и независимой многоцентровой валидации до рутинного внедрения в широкую современную клиническую практику повсеместно.

Ключевые слова: фармакорезистентная эпилепсия, низкоинтенсивный фокусированный ультразвук, транскраниальная ультразвуковая стимуляция, нейромодуляция,

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эпилептогенная сеть, акустическое моделирование, зона начала приступа, стереоэлектроэнцефалография.

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FARMAKOREZISTENT EPILEPSIYADA PAST INTENSIVLIKDAGI FOKUSLANGAN ULTRATOVUSH: TARMOQ NISHONLASH, AKUSTIK DOZANI NAZORAT QILISH VA QAYTAR NOINVAZIV NEYROMODULYATSIYA

Annotatsiya

Dolzarblik. Farmakorezistent epilepsiya takroriy tutqanoqlar, jarohatlar, kognitiv pasayish, psixososial moslashuv buzilishi va muddatidan oldingi o'lim bilan bog'liq bo'lib qolmoqda. Rezektiv jarrohlik hamda implantatsion neyrostimulyatsiya samarali bo'lishi mumkin, biroq ko'plab bemorlarda ikki tomonlama, chuqur, multifokal, funksional muhim korteksda joylashgan yoki yetarlicha lokalizatsiya qilinmagan epileptogen tarmoqlar invaziv davolashni cheklaydi. Past intensivlikdagi fokuslangan ultratovush kortikal va subkortikal tuzilmalarni notermik, kesmasiz va yuqori aniqlikda modulyatsiya qilish imkonini beradi.

Material va usullar. Strukturaviy narrativ sharh 2026-yil iyuligacha mavjud bo'lgan prospektiv tadqiqotlar, pilot sinovlar, preklinik tajribalar, texnik ishlanmalar, xavfsizlik bo'yicha konsensus tavsiyalari va ro'yxatdan o'tgan protokollarni birlashtirdi. Dalillar mexanizm, akustik doza, kalla suyagidan o'tish, nishonni tanlash, elektrofiziologik ta'sir, klinik samaradorlik, xavfsizlik, takrorlanuvchanlik va joriy etish bo'yicha tizimlashtirildi. Radikal rezeksiya uchun mos kelmaydigan farmakorezistent fokal epilepsiyali kattalarda prospektiv ko'p markazli randomizatsiyalangan ikki tomonlama ko'r soxta muolaja nazoratli tadqiqot taklif etildi.

Natijalar. Insondagi pilot tadqiqotlar sonikatsiyani tutqanoq boshlanish zonasiga radiologik shikastlanishsiz yetkazish va intrakranial elektroensefalografik faollikni o'zgartirish mumkinligini ko'rsatadi, biroq tutqanoq natijalari dastlabki va geterogenligicha qolmoqda. Ta'sir yo'nalishi tashuvchi chastota, impuls davomiyligi, takrorlanish chastotasi, ish sikli, bosim, ekspozitsiya davomiyligi, nishon geometriyasi va miya holatiga bog'liq. Birlamchi yakuniy nuqta to'rtinchi–oltinchi oylarda davolash bilan bog'liq nevrologik yomonlashuvsiz nogiron qiluvchi tutqanoqlar chastotasi kamida ellik foiz kamaygan bemorlar ulushidir. Ikkilamchi ko'rsatkichlar tutqanoqsizlik, elektrografik yuklama, kognitsiya, kayfiyat, hayot sifati, nishon faollashuvi biomarkerlari, akustik ekspozitsiya, nojo'ya hodisalar va ta'sir davomiyligini qamrab oladi.

Xulosa. Ushbu usul individual akustik modellashtirish, soxta nazorat, mexanistik biomarkerlar, standartlashtirilgan xavfsizlik hisoboti va mustaqil ko'p markazli validatsiyani talab qiladigan eksperimental tarmoq neyromodulyatsiyasi bo'lib qolmoqda odatiy klinik amaliyotga keng joriy etishdan oldin.

Kalit so'zlar: farmakorezistent epilepsiya, past intensivlikdagi fokuslangan ultratovush, transkranial ultratovush stimulyatsiyasi, neyromodulyatsiya, epileptogen tarmoq, akustik modellashtirish, tutqanoq boshlanish zonasi, stereoelektroensefalografiya.

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Introduction. Drug-resistant epilepsy is defined by the persistence of seizures despite appropriately chosen, tolerated, and adequately administered trials of at least two antiseizure-medication regimens. It represents a biologically and clinically heterogeneous group encompassing mesial temporal lobe epilepsy, neocortical focal epilepsy, structural epilepsy, developmental and epileptic encephalopathies, multifocal epilepsy, and epilepsies without a clearly visible structural lesion. Persistent seizures are associated with traumatic injury, progressive restrictions on education and employment, cognitive and psychiatric comorbidity, medication toxicity, social isolation, sudden unexpected death in epilepsy, and substantial caregiver burden [1, 2, 3]. Resective or disconnective epilepsy surgery provides the highest probability of durable seizure freedom when a sufficiently localized epileptogenic zone can be removed without unacceptable neurological impairment. Nevertheless, many patients are not suitable surgical candidates because seizure-generating tissue is bilateral, multifocal, deep, poorly localized, or inseparable from eloquent cortical and subcortical networks. Others decline resection because of concern regarding language, memory, visual-field, motor, affective, or personality-related consequences [3, 6, 10]. Implantable neuromodulation, including vagus nerve stimulation, anterior thalamic deep brain stimulation, and responsive neurostimulation, provides clinically meaningful seizure reduction for selected patients. These therapies usually reduce rather than eliminate seizures and require surgery, implanted leads, pulse generators, programming, battery management, and long-term device surveillance. Their effectiveness can improve progressively over several years, suggesting that neuromodulation may alter distributed epileptic networks rather than merely interrupt individual seizures [5, 11, 16]. Low-intensity focused ultrasound represents a conceptually different strategy. Acoustic energy is transmitted through the intact scalp and skull and concentrated within a cortical or subcortical target. Unlike high-intensity focused ultrasound, which produces irreversible thermal ablation, low-intensity transcranial ultrasound stimulation is intended to modify neural activity without creating a structural lesion. Unlike transcranial magnetic or direct-current stimulation, ultrasound can potentially reach the hippocampus, thalamus, insula, cingulate cortex, and other deep targets while maintaining a comparatively restricted focal field [4, 7, 14].

The term “low intensity” does not define a single intervention. Neuromodulatory outcome depends on carrier frequency, acoustic pressure, spatial-peak temporal-average intensity, pulse duration, pulse-repetition frequency, duty cycle, number of pulses, intersonication interval, total exposure duration, transducer geometry, focal volume, tissue properties, skull attenuation, and the electrophysiological state of the targeted network. Different combinations may produce excitation, inhibition, mixed effects, or no detectable neural response [8, 9, 25]. This parameter dependence is especially important in epilepsy. An insufficient acoustic dose may fail to engage the epileptogenic network, whereas an excitatory or poorly timed pattern could theoretically facilitate epileptiform activity. In a preclinical study, repetitive ultrasound delivered with one interburst interval suppressed epileptic activity, while a shorter interval worsened epileptiform activity despite otherwise related stimulation parameters. The observation emphasizes that ultrasound should not be treated as intrinsically anticonvulsant; its biological effect depends on dose, timing, state, and target [10, 13, 23]. The first prospective human studies have demonstrated that low-intensity sonication can be directed to seizure-onset tissue and can modify intracranial electrophysiological activity without producing visible

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edema or tissue destruction. However, these studies included only a small number of participants, used heterogeneous targets and protocols, and were designed primarily to assess feasibility and safety rather than definitive seizure efficacy [2, 3, 18]. The six-participant stereo-electroencephalography study reported heterogeneous short-term seizure responses, including seizure-frequency reduction in two participants and increased subclinical seizures in another, underscoring the need for controlled dose optimization. Since 2024, clinical development has expanded from isolated feasibility studies to open-label multicenter protocols, dose-comparison studies, and investigations using implanted responsive-neurostimulation electrodes as objective long-term electrophysiological monitors. Registered studies now evaluate unilateral or bilateral temporal lobe targets, repeated exposures, alternative dose schedules, and real-versus-sham sonication [6, 13, 28]. The purpose of this article is to synthesize the biological rationale, technical architecture, target-selection principles, clinical evidence, safety requirements, and translational limitations of low-intensity focused ultrasound in drug-resistant epilepsy. A prospective multicenter, randomized, double-blind, sham-controlled study is also proposed to distinguish true therapeutic effects from seizure variability, regression to the mean, diary bias, placebo effects, and nonspecific sensory consequences of sonication.

Materials and Methods. A structured narrative review was performed using evidence available through July 2026. Eligible evidence included prospective human trials, pilot safety studies, first-in-human investigations, stereo-electroencephalographic studies, preclinical epilepsy models, acoustic-modeling investigations, studies of human deep-brain target engagement, international safety and reporting recommendations, and registered clinical protocols. Evidence was grouped into nine domains: biological plausibility, acoustic parameterization, skull transmission, anatomical targeting, electrophysiological target engagement, clinical seizure outcomes, neuropsychological outcomes, biophysical safety, and implementation feasibility. High-intensity ablative focused ultrasound and microbubble-mediated blood–brain barrier opening were reviewed only to distinguish their mechanisms and safety requirements from nonablative neuromodulation. The clinical population of interest comprised adults with drug-resistant focal epilepsy in whom seizures persisted despite at least two appropriately selected antiseizure-medication regimens. Particular emphasis was placed on patients unsuitable for curative resection because of bilateral temporal lobe epilepsy, deep or eloquent epileptogenic tissue, multifocality, uncertain epileptogenic-zone boundaries, previous unsuccessful surgery, or unwillingness to undergo tissue-destructive treatment.

Clinical efficacy outcomes included median percentage change in monthly disabling-seizure frequency, responder rate defined by at least 50% seizure reduction, seizure freedom, reduction in focal-to-bilateral tonic–clonic seizures, seizure-cluster frequency, rescue-medication use, emergency attendance, and seizure-related injury. Electrographic outcomes included interictal epileptiform-discharge rate, electrographic-seizure burden, high-frequency oscillations, spectral-power change, network connectivity, and seizure-onset propagation. Safety outcomes included new neurological deficit, cognitive deterioration, mood or behavioral change, headache, dizziness, nausea, scalp discomfort, auditory symptoms, thermal sensation, seizure exacerbation, status epilepticus, edema, hemorrhage, ischemia, blood–brain barrier disturbance, and structural MRI abnormalities. Acoustic reporting was evaluated according to transducer characteristics, free-field exposure, skull-adjusted in situ exposure, pulse timing, focal geometry, thermal estimates, and mechanical indices [11, 12, 20].

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Proposed original study. A prospective, multicenter, randomized, double-blind, sham-controlled trial is proposed for adults aged 18–70 years with drug-resistant focal epilepsy. Participants would be required to have at least four countable disabling seizures during an eight-week baseline period and a stable antiseizure-medication regimen for at least four weeks before randomization. Eligible participants would have a predefined target supported by concordant clinical semiology, scalp EEG, structural MRI, positron-emission tomography, single-photon emission computed tomography, magnetoencephalography, stereo-electroencephalography, or chronic implanted-electrode recordings. Participants suitable for curative resection with an acceptable predicted neurological risk would not be enrolled unless they had declined surgery after formal multidisciplinary counseling. Exclusion criteria would include progressive intracranial disease, unstable psychiatric illness, pregnancy, uncontrolled coagulopathy, severe skull abnormality preventing reliable acoustic transmission, active scalp infection, recurrent status epilepticus, recent major medication changes, inability to maintain a seizure diary, or an implanted device incompatible with the ultrasound or imaging protocol. Randomization would be stratified by unilateral versus bilateral epilepsy, temporal versus extratemporal target, previous epilepsy surgery, and baseline focal-to-bilateral tonic–clonic seizure frequency. Participants would receive active sonication or sham treatment in identical sessions. The sham condition would reproduce positioning, coupling, equipment sounds, session duration, and operator interaction without delivering a therapeutic intracranial acoustic field. The proposed primary endpoint would be the proportion of participants achieving at least 50% reduction in monthly disabling-seizure frequency during months four through six compared with baseline, without persistent treatment-related neurological or neuropsychological deterioration. A delayed primary assessment is preferred because short post-treatment intervals can be distorted by peri-interventional stress, medication adherence, natural seizure clustering, and transient electrophysiological effects.

Secondary endpoints would include median seizure reduction, seizure freedom, focal-to-bilateral tonic–clonic seizure reduction, electrographic-seizure burden, interictal activity, quality of life, depression and anxiety, memory, language, executive function, sleep, work participation, caregiver burden, and patient global impression of change. Target-engagement outcomes would include acute and delayed changes in intracranial EEG when available, scalp EEG source-localized activity, resting-state functional MRI, arterial-spin-labeling perfusion, magnetic resonance spectroscopy, and network-connectivity metrics. Individual acoustic simulations would estimate pressure, intensity, focal-volume overlap, skull heating, intracranial off-target exposure, and accumulated dose for every participant.

Results. The mechanisms underlying ultrasound neuromodulation are incompletely resolved and probably involve several interacting processes. Acoustic radiation force can deform neural membranes and extracellular structures. Cyclic pressure variations may modify membrane capacitance, alter lipid-bilayer mechanics, and influence mechanosensitive or voltage-gated ion channels. Additional hypotheses include intramembrane cavitation, changes in synaptic vesicle release, modulation of glial activity, altered neurovascular coupling, and small temperature-dependent changes that remain below the threshold for tissue ablation [9, 12, 22]. The relative contribution of each mechanism depends on acoustic parameters and the cellular composition of the target. Neurons, inhibitory interneurons, astrocytes, vascular cells, and axonal tracts may not respond identically to the

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same exposure. Consequently, a protocol that suppresses activity in one structure or animal model cannot be assumed to suppress another epileptogenic network. Preclinical epilepsy studies have reported reduction of chemically induced epileptiform discharges, suppression of recurrent seizures, modulation of local-field-potential dynamics, and changes in seizure-associated behavior. These effects have been demonstrated in acute pentylenetetrazol, kainic-acid, and other experimental models, but the protocols vary substantially in frequency, pressure, duty cycle, pulse duration, exposure schedule, anesthesia, and seizure model [15, 17, 27]. The direction of neural modulation cannot be predicted from total energy alone. Two protocols with similar spatial-peak temporal-average intensity may differ biologically because one uses short pulses at a high repetition frequency, while another uses longer pulses separated by extended intervals. Temporal structure may interact with endogenous oscillations, synaptic depression, inhibitory interneurons, glial signaling, and vascular responses. For epilepsy, the ideal exposure would suppress pathological synchronization while preserving physiological memory, language, attention, and sensorimotor processing. This objective is more complex than producing a generalized reduction in neuronal excitability. Excessive or spatially imprecise inhibition of the dominant hippocampus could impair episodic memory, whereas off-target modulation of limbic networks could alter mood, motivation, or emotional regulation.

Table 1. **Distinction between therapeutic ultrasound strategies**

Characteristic	**Low-intensity neuromodulatory ultrasound**	**High-intensity focused-ultrasound ablation**	**Microbubble-mediated BBB opening**
Primary objective	Reversible modulation of neural activity	Irreversible thermal lesioning	Transient increase in vascular permeability
Tissue destruction	Not intended	Intended within the thermal target	Not intended
Microbubbles	Usually absent	Absent	Required
Main mechanism	Mechanical and electrophysiological neuromodulation	Coagulative thermal necrosis	Stable cavitation and endothelial modulation
Principal epilepsy application	Suppression or reorganization of epileptogenic networks	Ablation or disconnection of a defined focus	Targeted delivery of antiseizure or biological agents
Repeatability	Potentially repeatable	Limited by permanent lesion	Potentially repeatable with vascular monitoring
Main safety concerns	Off-target excitation, heating, auditory effects, seizure aggravation	Hemorrhage, edema, irreversible neurological deficit	Hemorrhage, edema, sterile inflammation, excessive barrier disruption
Clinical maturity in epilepsy	Early pilot and feasibility phase	Case reports and early trials	Preclinical or exploratory

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Acoustic dose and the transcranial propagation problem. Acoustic dose in transcranial neuromodulation cannot be defined adequately by the voltage applied to the transducer or by free-water intensity alone. The skull absorbs, reflects, refracts, and distorts ultrasound. Transmission depends on skull thickness, density, curvature, internal heterogeneity, angle of incidence, target depth, transducer aperture, carrier frequency, and coupling quality [7, 14, 19]. Lower carrier frequencies generally penetrate the skull more effectively but produce a larger focal volume. Higher frequencies can improve spatial resolution but undergo greater attenuation and phase distortion. The optimal frequency is therefore a compromise between transmission, precision, and target accessibility. Single-element transducers are relatively simple but have limited electronic steering and may produce a comparatively elongated focal zone. Phased arrays can correct phase delays across individual elements, steer the focus electronically, and reduce off-target energy. Large-aperture helmet systems can potentially improve focal precision for deep targets but require more complex calibration, immobilization, coupling, computational planning, and quality assurance. A 256-element helmet-shaped system reported in 2025 used individualized planning and concurrent functional MRI to modulate the lateral geniculate nucleus and its connected visual network. The investigation was not an epilepsy trial, but it demonstrated that highly focal, nonablative modulation of a small human thalamic nucleus is technically achievable with advanced arrays and model-based correction. Direct electrophysiological evidence of deep target engagement has also been obtained in people with implanted deep-brain-stimulation electrodes. Targeted ultrasound altered local-field-potential activity within the globus pallidus, with effects varying according to stimulation protocol. These findings support the premise that transcranial ultrasound can modify deep human circuits rather than acting only through superficial auditory or somatosensory pathways. Nevertheless, target engagement in movement or visual circuits cannot be extrapolated automatically to seizure suppression. Epileptogenic networks demonstrate dynamic excitability, propagation, state dependence, sleep-related modulation, medication effects, and substantial interictal–ictal variability. The acoustic field must overlap a biologically relevant node while avoiding stimulation patterns that facilitate synchronization.

Table 2. **Acoustic parameters requiring prospective reporting**

Parameter	Biological or technical significance	Required reporting approach
Carrier frequency	Determines wavelength, skull penetration, attenuation, and focal dimensions	Report nominal and measured frequency
Peak negative pressure	Relates to mechanical exposure and potential neural effects	Report free-field and estimated in situ values
Pulse duration	Influences temporal integration and membrane deformation	Report duration of each acoustic pulse
Pulse-repetition frequency	Determines timing of repeated mechanical exposure	Report exact repetition rate
Duty cycle	Defines the fraction of time ultrasound is active	Report as percentage and calculate total on-time
Sonication duration	Influences cumulative neuromodulatory and thermal effects	Report each train and complete session duration

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Intertrain interval	May determine inhibitory or facilitatory network effects	Report timing between trains
Focal dimensions	Determines anatomical selectivity and off-target exposure	Report lateral and axial dimensions
Skull-adjusted intensity	More clinically relevant than water-tank output	Estimate with individualized acoustic modeling
Mechanical index	Used in assessment of mechanical bioeffect risk	Report free-field and transcranial estimates
Thermal dose	Estimates temperature-related tissue risk	Model brain, skull, and scalp exposure
Coupling and positioning	Affect transmission and reproducibility	Document coupling medium, immobilization, and neuronavigation error

International reporting and safety initiatives now emphasize detailed disclosure of transducer design, driving parameters, free-field measurements, pulse timing, in situ estimates, intensity definitions, thermal modeling, and mechanical exposure. Without such standardization, two studies described simply as “low-intensity ultrasound” may deliver biologically different interventions [16, 23, 30]. The published ITRUSST recommendations provide a framework for reproducible application but do not replace disease-specific risk assessment. Target selection: focus, node, or network Traditional epilepsy surgery attempts to identify an epileptogenic zone whose removal is both necessary and sufficient for seizure freedom. Focused-ultrasound neuromodulation may require a broader conceptual framework because temporary modulation of a network node does not necessarily eliminate the pathological system. Potential targets include the seizure-onset zone, hippocampus, amygdala, insula, neocortical focus, anterior nucleus of the thalamus, centromedian nucleus, medial pulvinar, subiculum, entorhinal cortex, and propagation hubs identified through connectomic analysis. The best target may vary according to epilepsy phenotype. For unilateral mesial temporal lobe epilepsy, the hippocampus is a biologically plausible target, particularly when resection is contraindicated or refused. However, hippocampal sclerosis, atrophy, calcification, temporal-bone thickness, air-containing mastoid cells, and target depth can alter ultrasound delivery. Bilateral temporal lobe epilepsy raises the additional risk of bilateral memory-network disruption. In neocortical epilepsy, the seizure-onset zone may be close to language, motor, visual, or association cortex. A small focal field may provide an advantage over diffuse electrical stimulation, but targeting uncertainty of only several millimeters could expose an eloquent cortical area. Functional MRI, tractography, magnetoencephalography, navigated stimulation, and neuropsychological lateralization should therefore be integrated into planning. Thalamic targets may be appropriate for multifocal or generalized network epilepsies. The anterior nucleus participates in limbic circuitry and is an established electrical deep-brain-stimulation target. The centromedian nucleus and medial pulvinar participate in widespread thalamocortical propagation and arousal networks. Focused ultrasound could permit noninvasive testing of target responsiveness before permanent implantation, although repeated sessions may be required to maintain efficacy. A practical target-selection strategy should distinguish

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the anatomical seizure-onset zone, the minimum effective modulation volume, the functional tissue that must be spared, and the propagation network that determines clinical seizure expression. Targeting only the earliest electrographic contact may fail when that contact represents an accessible recording site rather than the complete epileptogenic substrate.

Clinical evidence. The prospective Epilepsia pilot study enrolled six patients with drug-resistant epilepsy undergoing stereo-electroencephalography. Ultrasound was directed to the seizure-onset zone under neuronavigational guidance, while intracranial activity was recorded during and after sonication. The protocol used a ceiling spatial-peak temporal-average intensity of 2.8 W/cm², a 30% duty cycle, and a ten-minute modulation period [10, 15, 16]. Two participants demonstrated reduced seizure frequency during the three-day observation period, while one experienced an increase in subclinical seizures. Post-treatment MRI showed neither a new structural lesion nor cerebral edema. One participant reported scalp heating, and another developed transient naming and memory impairment that resolved within three weeks. Significant spectral-power changes occurred at targeted stereo-electroencephalographic contacts, providing evidence of local electrophysiological engagement [21, 24, 31]. The study was not designed to establish durable seizure efficacy. The sample was small, follow-up was brief, there was no sham group, and participants underwent invasive monitoring that may itself alter seizure behavior. Nevertheless, the combination of individualized targeting and intracranial electrophysiology provided a valuable mechanistic bridge between animal studies and outpatient therapeutic trials.

A separate 2024 pilot safety report evaluated hippocampal transcranial ultrasound in six patients with drug-resistant epilepsy. The study supported feasibility and identified a preliminary seizure-reduction signal, but its uncontrolled design and small cohort prevent causal conclusions. Functional-connectivity changes appeared more prominent in patients with larger clinical improvement, suggesting that network imaging might eventually serve as a response biomarker [11, 16, 23]. The current clinical pipeline includes several complementary designs. NCT06388707 evaluates safety, tolerability, and preliminary efficacy in unilateral or bilateral drug-resistant temporal lobe epilepsy using a prospective open-label multicenter design. NCT06492720 uses a randomized two-arm dose-comparison framework. NCT05947656 evaluates neuronavigation-guided sonication of one or both hippocampi. NCT07353918 includes patients with implanted responsive neurostimulation systems and compares active with sham intervention while using chronic intracranial recordings to monitor electrographic effects [1, 10, 13].

Table 3. **Selected human evidence and current clinical-development directions**

Study or protocol	Population	Target and design	Principal contribution	Main limitation
Lee et al., 2022	Six patients with DRE undergoing SEEG	Neuronavigation-guided sonication of the seizure-onset zone	Demonstrated intracranial target engagement and absence of MRI-visible tissue injury	Very small uncontrolled sample and brief follow-up

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Bubrick et al., 2024	Six patients with drug-resistant epilepsy	Repeated hippocampal transcranial ultrasound	Supported feasibility and preliminary clinical signal	No definitive efficacy comparison
NCT03868293	Adults with drug-resistant temporal lobe epilepsy	Repeated pulsed LIFU targeting the affected hippocampus	Evaluates serial treatment and seizure-frequency change	Open-label single-group design
NCT05947656	Drug-resistant temporal lobe epilepsy	NaviFUS treatment of one or both hippocampi	Evaluates neuronavigation-guided treatment feasibility	Early-phase study
NCT06388707	Unilateral or bilateral drug-resistant TLE	Prospective open-label multicenter pilot	Tests safety and preliminary efficacy across centers	No sham comparator
NCT06492720	Drug-resistant epilepsy	Randomized low-dose versus high-dose protocol	Provides dose-comparison information	Open-label treatment allocation
NCT07353918	Medically refractory TLE with implanted RNS electrodes	Active versus sham LIFU with chronic intracranial monitoring	Enables objective electrographic target-engagement assessment	Restricted population with existing implanted device

Safety and adverse-effect surveillance. Safety evaluation must distinguish thermal injury, mechanical injury, unintended neuromodulation, and disease-specific seizure risk. The absence of contrast microbubbles reduces the likelihood of cavitation-related vascular injury, but skull heating, focal tissue heating, standing-wave formation, off-target exposure, and cumulative-session effects remain relevant. The mechanical index alone is insufficient because it does not capture all pulse-timing, cumulative, skull, and focal-field effects. Safety assessment should include calibrated free-field pressure, individualized in situ estimates, temperature modeling, thermal dose, acoustic coupling, focal overlap with vascular structures, and device-output verification. The 2025 ITRUSST biophysical-safety consensus proposed exposure conditions considered to represent nonsignificant biophysical risk in appropriate research contexts. These recommendations are not equivalent to regulatory approval and do not establish that a given protocol is clinically safe in epilepsy. A disease capable of spontaneous seizure clustering and status epilepticus requires additional neurological surveillance beyond generic ultrasound safety metrics. Clinical monitoring should include neurological examination, memory, language, attention, executive function, mood, sleep, seizure frequency, and rescue-medication use. MRI with susceptibility-weighted, diffusion-weighted, T2-weighted, and fluid-attenuated inversion-recovery sequences should be obtained when clinically appropriate to detect hemorrhage, ischemia, edema, or unexpected tissue alteration. Auditory and somatosensory confounds are methodologically

and clinically relevant. Pulsed ultrasound can produce perceived sound through bone conduction or activate peripheral pathways. A participant who distinguishes active from sham treatment may alter seizure reporting, anxiety, sleep, and adherence. Auditory masking, credible sham design, and post-session blinding assessment should therefore be included. Repeated exposure introduces questions not answered by single-session safety studies. A protocol that is safe once may produce cumulative plasticity, subtle cognitive effects, progressive scalp irritation, or repeated seizure destabilization. Longitudinal studies should include predefined stopping rules for seizure worsening, status epilepticus, new psychiatric symptoms, persistent cognitive decline, or unexpected MRI abnormalities.

Proposed multicenter randomized trial. The proposed trial would include an eight-week baseline period, individualized acoustic planning, randomization to active or sham treatment, and repeated sessions delivered under identical conditions. A minimum six-month blinded follow-up would be followed by an optional open-label extension. Active treatment would use a standardized parameter family but permit prespecified skull- and target-adjusted pressure correction. This approach would reduce variation in intracranial exposure without allowing unrestricted site-level parameter modification. All acoustic simulations and delivered-output logs would be transferred to an independent core laboratory. The sham transducer would reproduce contact pressure, coupling, positioning, audible equipment cues, and session duration. Neither the participant, treating epileptologist, outcome assessor, nor diary-review committee would know allocation. The ultrasound engineer could remain unblinded only if required for device safety and would have no role in clinical assessment. Seizure outcomes would be adjudicated from diaries, caregiver reports, ambulatory EEG, wearable events, and implanted recordings where available. An independent committee would classify events as focal aware, focal impaired-awareness, focal-to-bilateral tonic–clonic, nonepileptic, uncertain, or electrographic-only.

Table 4. **Proposed study protocol and originality**

Component	**Proposed specification**
Population	Adults with drug-resistant focal epilepsy unsuitable for or declining curative resection
Design	Multicenter, randomized, double-blind, sham-controlled, parallel-group trial
Baseline period	Eight weeks with stable medication and prospective seizure recording
Intervention	Repeated individualized LIFU sessions directed to a prespecified epileptogenic-network target
Comparator	Credible sham sonication with identical workflow and sensory environment
Primary endpoint	At least 50% reduction in disabling seizures during months 4–6 without persistent neurological deterioration
Secondary clinical endpoints	Seizure freedom, median reduction, tonic–clonic seizures, injuries, rescue treatment, quality of life
Neuropsychological endpoints	Memory, language, executive function, mood, sleep, and patient-reported cognition

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Electrophysiological endpoints	Interictal discharges, electrographic seizures, high-frequency oscillations, network connectivity
Acoustic endpoints	Skull-adjusted pressure, intensity, focal overlap, thermal estimate, targeting error, accumulated exposure
Safety endpoints	Seizure worsening, status epilepticus, MRI abnormality, neurological deficit, psychiatric change, scalp injury
Blinding assessment	Participant and investigator estimation of treatment allocation after each session
External validation	Locked protocol replicated at independent epilepsy centers and across skull-density strata
Originality	Direct integration of clinical response, mechanistic target engagement, acoustic dose, and neuropsychological safety

Discussion. Low-intensity focused ultrasound is attractive for drug-resistant epilepsy because it offers a combination not provided by existing treatments: noninvasive access to both superficial and deep structures, potentially restricted focal exposure, reversibility, repeatability, and compatibility with electrophysiological or imaging biomarkers. These properties could fill an important therapeutic gap for patients who are unsuitable for resection and reluctant or unable to undergo permanent device implantation. Current evidence, however, supports feasibility rather than established efficacy. The human literature consists mainly of small pilot studies, short follow-up, heterogeneous targets, and variable acoustic parameters. Seizure reduction observed after treatment may reflect true neuromodulation, natural fluctuation, regression to the mean, medication adherence, hospital-related behavioral changes, or reporting bias. Epilepsy is particularly vulnerable to erroneous efficacy conclusions because seizure frequency varies over circadian, multidien, hormonal, sleep-related, and stress-related cycles. Baseline periods that are too short can enroll participants during an unusually severe phase, producing apparent improvement even without active treatment. Randomization, sufficiently long baselines, sham control, and blinded adjudication are therefore essential.

The first major translational problem is parameter selection. Ultrasound publications frequently use terms such as “low intensity,” “pulsed,” or “theta burst” without enough information to reconstruct the delivered intracranial exposure. Standardized reporting should include transducer geometry, carrier frequency, calibrated pressure, pulse timing, duty cycle, coupling, skull model, in situ estimate, focal dimensions, thermal estimate, and cumulative exposure [3, 10, 18, 27]. The second problem is biological directionality. An ultrasound protocol cannot be assumed to inhibit the target because it uses a low average intensity. Parameter-dependent excitation and inhibition have been demonstrated across experimental systems, while preclinical epilepsy work shows that changing temporal pattern can reverse the direction of the effect. Early human trials should therefore include electrophysiological target-engagement measurements before advancing to large efficacy studies. The third problem is target definition. A seizure-onset zone identified by the earliest stereo-electroencephalographic activity may not equal the complete epileptogenic network. Sonication of a small region may alter local spectral power without preventing seizure propagation. Conversely, modulation of a strategic thalamic or limbic hub might reduce widespread seizures even when the cortical onset remains unchanged. Patient-

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specific network analysis may improve target selection. Structural connectivity, resting-state functional MRI, ictal propagation, interictal high-frequency oscillations, and stimulation-response mapping can identify nodes with disproportionate influence on seizure spread. The optimal target may be the node with the highest predicted network-control value rather than the tissue with the earliest visible discharge.

Repeated sonication could be individualized in several ways. A fixed target could receive scheduled maintenance sessions, treatment could be timed to high-risk multidien seizure phases, or sonication could be triggered by electrographic biomarkers. The 2026 protocol involving patients with responsive-neurostimulation systems is particularly relevant because implanted electrodes can provide objective longitudinal measurements before and after real or sham ultrasound. Closed-loop focused ultrasound remains technically challenging. Real-time detection must be integrated with transducer positioning, acoustic coupling, treatment planning, and safety checks. Unlike an implanted electrical pulse, ultrasound cannot necessarily be delivered instantaneously during unrestricted daily activity with current clinical platforms. Portable or wearable transducers may eventually reduce this limitation, but stable skull coupling and focal accuracy must be maintained. Another potential role is preoperative functional testing. Temporary sonication of a proposed target could estimate whether its modulation alters seizures, memory, mood, or language before irreversible ablation or implantation. A favorable physiological response might support subsequent surgery, whereas cognitive deterioration could redirect the treatment plan. Such a “virtual lesion” paradigm requires rigorous validation because temporary modulation may not predict the effects of chronic stimulation or permanent destruction. LIFU should not be positioned as a replacement for evidence-based resective surgery in patients with a well-localized, safely resectable epileptogenic lesion. Delaying curative surgery in favor of an unproven noninvasive intervention could prolong seizure exposure and reduce the probability of optimal recovery. Appropriate candidates are more likely to be patients without a favorable resection option, those requiring network-level palliation, or those enrolled in carefully controlled presurgical investigations. Comparative effectiveness will ultimately be required. For mesial temporal lobe epilepsy, LIFU may be compared with laser interstitial thermal therapy, open resection, responsive neurostimulation, or continued medical therapy. For multifocal epilepsy, comparisons may involve vagus nerve stimulation, thalamic deep brain stimulation, or responsive-network approaches. The safety advantage of avoiding surgery should also be evaluated realistically. Noninvasive treatment eliminates risks associated with craniotomy, intracranial electrodes, infection, and implanted hardware, but it introduces different risks: inaccurate targeting, off-target modulation, skull heating, repeated exposure, unrecognized excitation, cognitive effects, and delayed seizure worsening. “Incisionless” does not mean biologically inactive or risk free. Neuropsychological outcomes deserve equal status with seizure frequency. A treatment that reduces seizures while impairing verbal memory, naming, executive control, or mood may not produce a favorable net benefit. This concern is especially important for dominant temporal and bilateral hippocampal targets. The primary endpoint proposed in this article combines seizure response with neurological safety. Traditional responder rates can misclassify a participant with a 50% seizure reduction and major memory decline as a treatment success. A composite net-benefit framework is more appropriate for interventions directed at eloquent neural networks.

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Blinding must be tested rather than assumed. Participants should be asked after each session whether they believe they received active or sham treatment and why. Scalp sensations, audible cues, equipment behavior, and operator interactions must be standardized. If blinding fails, objective electrographic endpoints become even more important. Statistical analysis should model seizure counts using methods appropriate for overdispersed recurrent events, such as negative-binomial mixed-effects models. Prespecified sensitivity analyses should address missing diaries, seizure clusters, medication changes, rescue therapy, and COVID-like external disruptions. The responder endpoint should be supplemented by continuous seizure-frequency change to avoid loss of information. Subgroup analyses should examine unilateral versus bilateral temporal epilepsy, MRI-positive versus MRI-negative disease, previous surgery, skull-density characteristics, target depth, focal-overlap accuracy, and baseline network connectivity. These analyses must be considered exploratory unless independently replicated. Equity and scalability also require attention. Individual CT-based acoustic simulation, MRI guidance, multidisciplinary epilepsy evaluation, and specialized ultrasound equipment may concentrate treatment in high-resource centers. Simplified workflows should not be adopted until their targeting accuracy and safety are demonstrated across diverse skull anatomy and healthcare environments. Data transparency will be essential. Negative or paradoxical electrophysiological responses should be reported, not only successful sonications. Acoustic simulation files, parameter definitions, target coordinates, and deidentified outcome data should be made available where ethically and legally possible. External replication is unlikely if essential device settings remain proprietary. The regulatory pathway will depend on the intended claim. A device intended for temporary network testing requires a different evidentiary framework from one claiming long-term seizure reduction. Changes in software, acoustic correction, pulse sequence, or transducer geometry may materially change biological exposure and cannot be treated as trivial engineering updates. Several limitations of the present review should be acknowledged. The evidence is heterogeneous and dominated by early-phase studies. The long-term effects of repeated treatment remain uncertain. Direct comparisons among hippocampal, cortical, and thalamic targets are unavailable. Published seizure outcomes may be influenced by selection and reporting bias. Registered trials remain ongoing, and their eventual results may change current conclusions. Despite these limitations, focused ultrasound provides a valuable experimental platform for causal investigation of human epileptic networks. It can combine precise anatomical targeting with EEG, stereo-electroencephalography, functional MRI, perfusion imaging, and neuropsychological testing. This combination may improve not only therapy but also understanding of which network nodes sustain seizures and which acoustic exposures produce inhibition rather than excitation.

Conclusion. Low-intensity focused ultrasound is an emerging, nonablative neuromodulation technology with potential applications in drug-resistant epilepsy. Its principal advantages are incisionless delivery, access to deep structures, relatively focal targeting, repeatability, and compatibility with electrophysiological and imaging biomarkers. Preclinical studies support the possibility of suppressing epileptiform activity, while early human investigations demonstrate that ultrasound can be directed to seizure-onset tissue, modify intracranial electrophysiological activity, and avoid overt structural injury under studied conditions. Clinical seizure outcomes remain preliminary, heterogeneous, and insufficient to establish therapeutic effectiveness. The central

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translational challenge is not simply to deliver ultrasound to the brain. It is to deliver a reproducible, skull-adjusted acoustic dose to a biologically appropriate epileptogenic-network node using parameters that inhibit pathological activity without impairing physiological cognition, language, mood, or sensorimotor function. Future studies require randomized sham-controlled designs, sufficiently long baseline and follow-up periods, individualized acoustic simulation, objective electrophysiological target-engagement biomarkers, systematic neuropsychological testing, transparent adverse-event reporting, and independent multicenter validation. Until these requirements are met, low-intensity focused ultrasound should remain an investigational strategy offered within ethically approved clinical trials rather than a routine substitute for established epilepsy surgery or implantable neuromodulation.

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