

**REVIEW**

Therapeutic Ultrasound: From Biophysical Mechanisms to Programmable and Closed-Loop Therapy

Kaidi Ren, Zhenyu Cao, Yile Fang* and Zhuhao Wu*

Nanjing Drum Tower Hospital, Clinical Medical College of Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine, Nanjing, China

*Corresponding Authors: Yile Fang. Email: fang1le@163.com; Zhuhao Wu. Email: zhuhao.wu@njglyy.com

Received: 17 September 2026; Accepted: 03 October 2026; Published: 27 October 2026

ABSTRACT: Therapeutic ultrasound is a non-invasive therapeutic platform that uses controlled acoustic energy to generate localized thermal, cavitation-mediated, and mechanical interactions in tissue. Its deep penetration, spatial selectivity, non-ionizing nature, and compatibility with image guidance support applications ranging from tissue ablation to reversible neuromodulation and externally controlled drug delivery. However, device performance is often reported without consistently linking acoustic input to the dominant local physical interaction and resulting therapeutic outcome. This Review therefore adopts a mechanism-to-therapy perspective. Acoustic parameters governing propagation, focusing, thermal deposition, cavitation, radiation force, streaming, and membrane permeabilization are first summarized. Representative modalities, including high-intensity focused ultrasound (HIFU) thermal ablation, histotripsy, neuromodulation, and ultrasound-mediated drug delivery, are then discussed with emphasis on mechanism-specific monitoring and control. Emerging advances in responsive biointerfaces, patient-specific field engineering, ultrasound-readable sensing, wearable systems, and adaptive actuation are further highlighted. Collectively, therapeutic ultrasound is progressing from one-way acoustic energy deposition toward programmable biophysical interventions that integrate field control, sensing, actuation, and feedback.

KEYWORDS: Therapeutic ultrasound; focused ultrasound; histotripsy; neuromodulation; drug delivery; closed-loop therapy

1 Introduction

Therapeutic ultrasound uses externally delivered acoustic energy to generate spatially confined physical interactions within biological tissues. The response elicited by therapeutic ultrasound is governed by the combined temporal waveform and spatial acoustic field rather than by any single exposure parameter. Frequency and pressure define fundamental wave characteristics, whereas pulse duration, pulse repetition frequency (PRF), duty cycle, cumulative exposure duration, and focusing determine how acoustic energy is distributed in space and time [1]. Continuous or high-duty-cycle exposures can generate thermal deposition and coagulative necrosis, whereas short high-pressure pulses can initiate cavitation and mechanical tissue fractionation. At lower exposures, radiation force, membrane deformation, bubble oscillation, acoustic streaming, and related mechanical effects can reversibly alter neural activity, vascular permeability, transport, or release from responsive materials [2]. These features provide non-invasive access to deep targets, spatially localized treatment, compatibility with real-time imaging, and increasing opportunities for wearable or biointegrated implementation. Nevertheless, the field remains fragmented across acoustics, clinical medicine,

neuroscience, drug delivery, biomaterials, and bioelectronics, and a mechanism-centered synthesis is needed to connect acoustic dose, local bioeffect, therapeutic endpoint, and safety window [3,4].

Previous reviews have largely focused on individual therapeutic modalities, specific anatomical applications, or particular device formats, including focused-ultrasound brain therapy and wearable ultrasound systems. In contrast, this Review adopts a mechanism-to-therapy framework that connects acoustic exposure, dominant local biophysical interactions, therapeutic outcomes, mechanism-specific monitoring, and emerging feedback control. Particular emphasis is placed on the convergence of acoustic engineering with drug delivery, responsive biomaterials, wearable biointerfaces, sensing, and adaptive actuation. Accordingly, the Review is organized as summarized in Fig. 1. It first introduces ultrasound generation, propagation, focusing, and the principal thermal and mechanical bioeffects, and then examines four representative therapeutic modalities: HIFU thermal ablation, histotripsy-mediated mechanical fractionation, low-intensity focused-ultrasound neuromodulation, and ultrasound-mediated drug delivery. Immune modulation and tissue regeneration are considered cross-cutting biological responses rather than independent acoustic modalities. The final section addresses quantitative dosimetry, mechanism-specific monitoring, patient-specific field engineering, intelligent wearables, and feedback control. The central argument is that the evolution of therapeutic ultrasound is defined not simply by increasing acoustic power, but by increasingly precise control over the spatial, temporal, and biological consequences of acoustic energy [5,6].

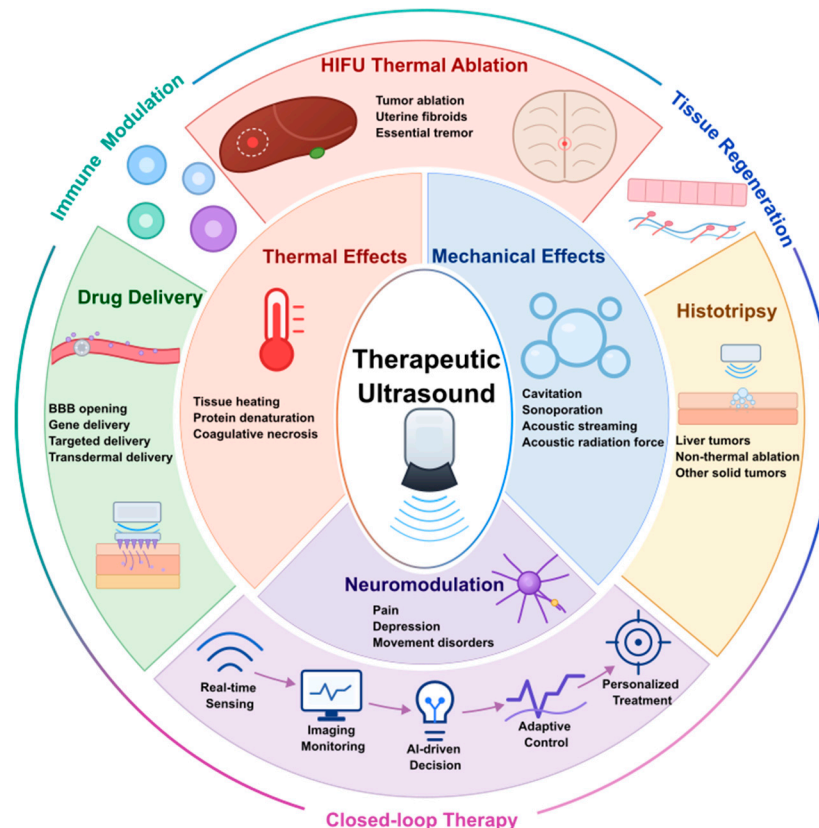


Figure 1: Biophysical mechanisms and therapeutic spectrum of ultrasound. Tunable acoustic parameters generate thermal and mechanical bioeffects that underpin HIFU thermal ablation, histotripsy-mediated mechanical tissue fractionation, neuromodulation, and ultrasound-mediated drug delivery. Immune modulation and tissue regeneration are cross-cutting biological responses, while sensing, imaging, AI-assisted decision making, and adaptive control are driving therapeutic ultrasound toward personalized closed-loop therapy.

2 Physical Principles and Biophysical Mechanisms of Therapeutic Ultrasound

2.1 Generation, Propagation and Focusing

Most therapeutic ultrasound systems use piezoelectric transducers to convert electrical excitation into acoustic pressure waves [1,7]. During propagation, ultrasound undergoes absorption, reflection, refraction, scattering, and attenuation, and the resulting *in situ* field can differ markedly from the nominal field at the transducer surface. Bone can produce reflection, phase aberration, and unintended heating, whereas gas-containing interfaces create large acoustic-impedance mismatches [2].

Therapeutic exposure should therefore be described using a set of complementary acoustic descriptors rather than nominal intensity alone. The spatial and temporal characteristics of an acoustic exposure are governed by different parameter groups. Frequency sets the wavelength and contributes to attenuation, penetration depth, and focal scale, whereas pressure amplitude is more directly associated with tissue deformation and the likelihood of cavitation. Pulse duration, pulse repetition frequency (PRF), duty cycle, and cumulative exposure duration collectively determine how acoustic energy is distributed over time. Curved transducers, acoustic lenses, phased arrays, holograms, and metasurfaces can further reshape the field in space, making both acoustic dose and field geometry central design variables for therapy [8–10].

2.2 Thermal Effects

Thermal effects arise when absorbed acoustic energy is converted into heat. Biological outcome depends on both temperature and exposure duration, and cumulative thermal-dose metrics are therefore more informative than acoustic power alone [9,11]. Mild hyperthermia can alter perfusion, membrane transport, and stress signaling, whereas sufficiently high thermal doses cause protein denaturation and coagulative necrosis. HIFU deliberately crosses this irreversible threshold within a confined focal volume while minimizing thermal injury along the propagation path.

Because heat diffuses beyond the nominal acoustic focus and is modified by perfusion, image-based treatment planning and thermal monitoring are integral to thermal therapy [12]. Magnetic-resonance thermometry can map temperature evolution during sonication and support adjustment of exposure so that the intended target receives an adequate thermal dose while adjacent structures remain within safety limits [13].

2.3 Mechanical Effects

Mechanical effects arise from acoustic momentum transfer and nonlinear interactions with tissue and bubbles [14]. Acoustic radiation force can produce displacement, strain, and membrane deformation, whereas cavitation can generate much larger localized stresses. Stable bubble oscillation produces microstreaming and shear, while inertial collapse can generate microjets, shock waves, and transient high-pressure events. Depending on exposure conditions, these effects can range from reversible membrane or vascular modulation to deliberate mechanical tissue destruction [15–17].

Acoustic streaming provides a further transport mechanism by introducing time-averaged convective flow into otherwise diffusion-dominated environments, particularly near oscillating bubbles, boundaries, sharp features, and microstructured interfaces [18]. Sonoporation similarly exploits localized mechanical stress to transiently increase cell-membrane permeability and facilitate intracellular transport [19]. These processes are discussed in greater detail in the application sections below; Fig. 2 is therefore limited to the fundamental acoustic descriptors and the broad classification of thermal, cavitation-related, and mechanical bioeffects. The major therapeutic modalities discussed below differ not only in their dominant

physical mechanisms but also in their monitoring requirements, safety constraints, and stage of clinical translation, as summarized in Table 1. These processes should not be regarded as equivalent hierarchical categories. Cavitation, acoustic radiation force, and acoustic streaming describe fundamental physical responses to acoustic excitation, whereas sonoporation is primarily a downstream biological consequence of localized mechanical stress. Depending on the exposure regime, membrane permeabilization may arise from bubble oscillation and collapse, microstreaming-induced shear, radiation-force-induced deformation, or combinations of these effects. Accordingly, Fig. 2 emphasizes the major physical mechanisms, while sonoporation is discussed as a mechanism-dependent biological outcome.

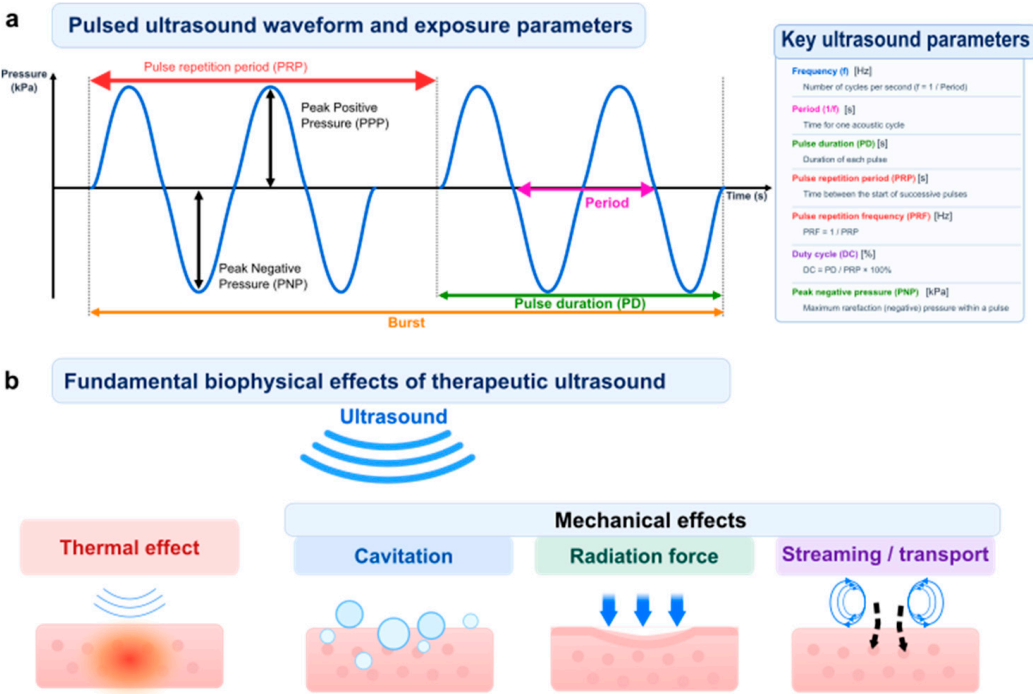


Figure 2: Fundamental acoustic descriptors and major biophysical effects of therapeutic ultrasound. (a) Representative pulsed-ultrasound waveform and the principal descriptors used to define acoustic exposure, including pressure amplitude, frequency, period, pulse duration, pulse-repetition period/frequency, and duty cycle. (b) Broad classification of ultrasound-induced bioeffects into thermal effects and mechanical effects, with the latter including cavitation, acoustic radiation force, and streaming-related transport.

Table 1: Comparison of major therapeutic ultrasound modalities, their dominant biophysical mechanisms, representative applications, monitoring strategies, safety considerations, and translational status.

Modality	Dominant Biophysical Mechanism	Representative Applications	Monitoring/Control	Major Safety Considerations	Translational Status
HIFU thermal ablation	Acoustic absorption and thermal deposition leading to coagulative necrosis	Essential tremor, uterine fibroids, prostate disease, selected solid tumors	MR thermometry; MRI/US guidance	Off-target heating, tissue-interface aberration, perfusion and motion	Established clinical use for selected indications

Table 1: *Cont.*

Modality	Dominant Biophysical Mechanism	Representative Applications	Monitoring/Control	Major Safety Considerations	Translational Status
Histotripsy	Cavitation-driven mechanical tissue fractionation	Liver tumors and non-thermal soft-tissue ablation	Bubble-cloud imaging; cavitation monitoring; US/MRI guidance	Off-target or prefocal cavitation, vascular/tissue injury	Clinical translation and ongoing investigation
Ultrasound neuromodulation	Radiation force and mechanically mediated membrane processes; additional mechanisms remain under investigation	Cortical and deep-brain modulation, movement disorders, pain and neural control	Acoustic field mapping, EEG, fMRI, neural recordings	Heating, auditory confounds, off-target stimulation	Clinical investigation and preclinical research
Ultrasound-mediated drug delivery	Barrier modulation, sonoporation, transport enhancement and acoustically triggered release	BBB opening, CNS delivery, gene delivery, transdermal delivery	Cavitation monitoring, imaging, transport/release measurements	Excessive cavitation, vascular injury, uncontrolled or off-target delivery	Clinical investigation to preclinical, depending on strategy

3 Therapeutic Modalities of Ultrasound

3.1 High-Intensity Focused Ultrasound Thermal Ablation

HIFU is among the most clinically mature therapeutic ultrasound modalities, with established or clinically implemented applications for several selected indications, although the degree of routine adoption differs among anatomical targets and healthcare systems. By concentrating acoustic energy within a millimeter-scale focal volume, HIFU can rapidly elevate local temperature above the threshold for irreversible protein denaturation and coagulative necrosis while largely sparing intervening tissue [20]. Clinical and investigational applications include MR-guided thalamotomy for medication-refractory essential tremor, uterine fibroids, localized prostate disease, painful bone lesions, and selected solid tumors [21–23]. The common therapeutic principle is not simply the delivery of high acoustic power, but the creation of a spatially confined and image-verifiable thermal dose.

Clinical precision depends on the complete acoustic and thermal pathway. Anatomical interfaces can distort phase and increase unintended heating, motion can displace targets, and tissue perfusion can remove heat from lesion margins [24]. MR thermometry and image-guided planning therefore provide a critical link between acoustic exposure and tissue outcome. Representative studies show that MR-guided HIFU can generate a localized temperature rise followed by a non-enhancing necrotic zone, while longitudinal imaging after thalamotomy or uterine-fibroid treatment demonstrates lesion evolution and tissue remodeling [12,25]. HIFU thus exemplifies mechanism-guided therapy supported by quantitative thermal dosimetry and image guidance, although aberration, motion, perfusion, and off-target heating remain important limitations. Representative image-guided HIFU applications are shown in Fig. 3.

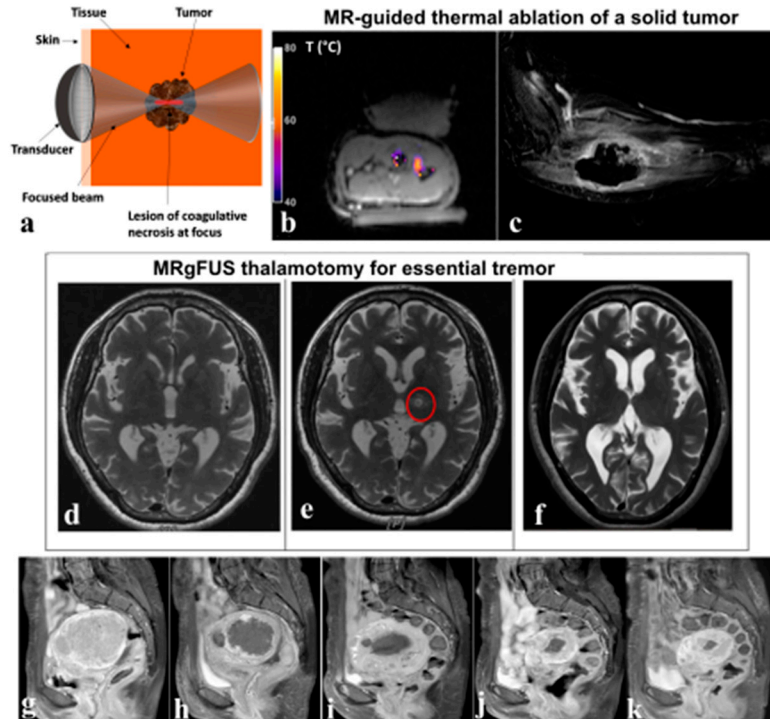


Figure 3: Image-guided HIFU thermal ablation and representative clinical applications. (a) Principle of focused thermal ablation and coagulative necrosis at the acoustic focus. Reproduced from Ref. [9]. Copyright 2020, MDPI. (b,c) MR-guided HIFU of a solid musculoskeletal lesion, showing intra-procedural MR thermometry and the post-treatment non-enhancing necrotic region. Adapted with permission from Ref. [25]. Copyright © 2022, Paolo Cabras et al. (d–f) Longitudinal MRI before, shortly after, and during follow-up after MR-guided focused-ultrasound thalamotomy for essential tremor. Adapted with permission from Ref. [26]. Copyright © 2021, Frontiers. (g–k) Longitudinal contrast-enhanced MRI of a uterine fibroid from baseline through long-term follow-up, illustrating progressive post-HIFU volume reduction. Reproduced with permission from Ref. [20]. Copyright © 2021, Florian Recker et al.

3.2 Histotripsy: Mechanical Tissue Fractionation

Histotripsy is a complementary ablation paradigm in which focused ultrasound mechanically fractionates tissue rather than thermally coagulating it. Several histotripsy pulse regimes have been developed, including intrinsic-threshold, shock-scattering, and boiling-based approaches. Although their pressure–time characteristics differ, each uses spatially confined bubble activity to mechanically disrupt tissue [27–29]. Efficacy therefore depends on the coupled behavior of acoustic exposure, bubble nucleation and growth, tissue mechanics, and confinement of the cavitation field.

The transition from bubble physics to clinical therapy is illustrated by image-guided liver histotripsy. The #HOPE4LIVER study translated this mechanism into liver-tumor treatment. Both primary and metastatic lesions were targeted without surgical access, and the echogenic cavitation cloud served as an intra-procedural indicator of the active treatment region. Post-treatment imaging showed a non-enhancing treatment zone that subsequently decreased in volume during follow-up [30]. These studies mark the transition of histotripsy from predominantly preclinical mechanical-ablation research toward clinical evaluation and implementation, particularly for liver tumors. However, treatment efficacy is not uniform across tissues or anatomical locations. Collagen-rich targets can resist fractionation, and transcranial applications are constrained by skull attenuation, aberration, and prefocal pressure amplification. Mapping

the transcranial treatment envelope has shown that some target locations are limited by off-target cavitation or insufficient focal pressure, while amplitude and phase correction can reduce prefocal hotspots and extend the accessible treatment profile [31,32]. These observations make histotripsy a particularly clear example of mechanism-linked therapy in which bubble dynamics, imaging feedback, and patient-specific field engineering must be considered together. These features, from cavitation-cloud dynamics to image-guided liver ablation and treatment-envelope engineering, are summarized in Fig. 4.

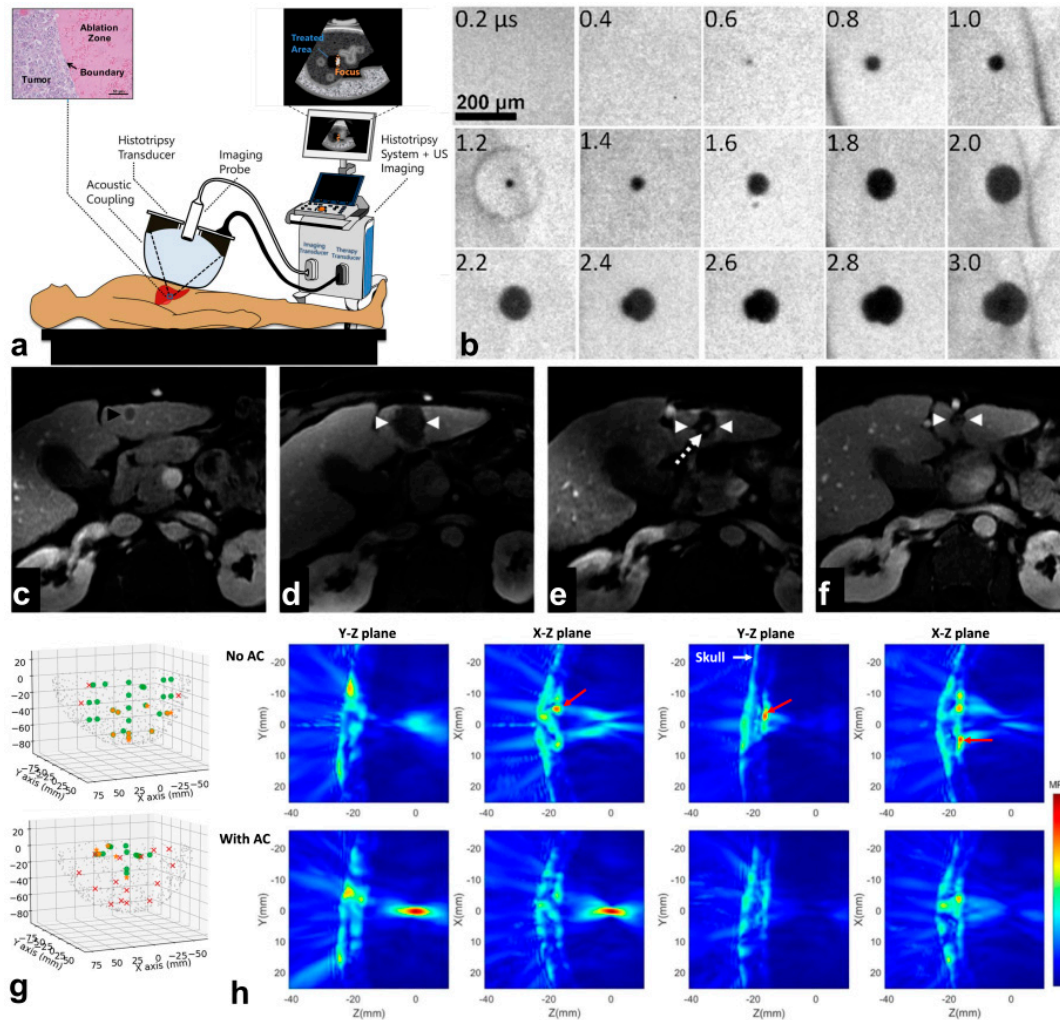


Figure 4: Histotripsy bubble physics, image-guided mechanical ablation, and treatment-envelope engineering. (a) Schematic overview of a non-invasive histotripsy procedure integrating therapy and imaging transducers, cavitation-cloud formation, and progressive tissue fractionation. Reproduced with permission from Ref. [17]. Copyright © 2019, Elsevier. (b) Representative high-speed bubble dynamics illustrating the physical basis of cavitation-mediated histotripsy. Reproduced with permission from Ref. [28]. Copyright © 2011, Acoustical Society of America. (c-f) Image-guided liver histotripsy showing the target before treatment, the intraprocedural bubble cloud, the early non-enhancing treatment zone, and follow-up involution. Reproduced from Ref. [30] under the terms of the CC BY 4.0 license. (g) Transcranial histotripsy treatment envelope illustrating on-target cavitation, prefocal cavitation, and inaccessible locations. (h) Simulated pressure fields before and after acoustic-field correction, demonstrating suppression of prefocal hotspots and improved focal confinement. (g,h) Reproduced with permission from Ref. [33]. Copyright © 2024, IOP.

3.3 Ultrasound Neuromodulation and Biointerface-Assisted Neural Control

In neuromodulation, focused ultrasound is operated below destructive exposure levels to modify neural activity while preserving tissue integrity. Compared with conventional non-invasive electrical and magnetic stimulation approaches, focused ultrasound offers the potential for millimeter-scale targeting of cortical and deep brain regions while remaining compatible with image guidance [34–37]. Human and animal studies have reported changes in cortical excitability, functional connectivity, neurochemical signaling, and behavior, but the direction and magnitude of response depend on pressure, frequency, pulse structure, stimulated volume, anatomy, and baseline neural state; nominal intensity alone is therefore insufficient to predict excitation or suppression [38–41]. Despite increasing investigation in human participants, ultrasound neuromodulation remains less clinically mature than thermal focused-ultrasound ablation, with many mechanistic and therapeutic applications still being evaluated in clinical or preclinical studies.

Several transduction mechanisms have been proposed, but the strength of evidence differs among them. These include radiation-force-induced membrane deformation, activation of mechanosensitive ion channels, changes in membrane capacitance, intramembrane cavitation, and small thermal contributions [34,42–44]. Experimental interpretation must also account for potential confounds such as bone-conducted auditory stimulation. These uncertainties have shifted attention from simple exposure reporting toward direct characterization of acoustic field geometry, target engagement, and downstream neural response [45,46].

Importantly, no single transduction mechanism currently explains all reported neuromodulatory responses across frequencies, pulse structures, anatomical targets, and experimental preparations. Radiation force and mechanically sensitive membrane processes have substantial experimental support, whereas contributions from intramembrane cavitation and other nonlinear mechanisms remain context dependent. Mechanistic claims should therefore be distinguished from phenomenological observations of neural activation or suppression, and exposure should be reported together with *in situ* field estimates and controls for auditory and thermal confounds. Recent advances can be organized around two converging trends. First, spatial field programming, including holographic transcranial stimulation and patterned retinal stimulation, enables distributed or arbitrarily shaped acoustic fields to recruit neural circuits beyond a single focus [7,47]. Second, biointerface-assisted transduction couples ultrasound to secondary electrical or cell-selective mechanisms, as illustrated by ultrasound-powered bioresorbable nerve-block systems and sonogenetic strategies [48,49]. Together, these approaches move neuromodulation from focal pressure delivery toward programmable spatial patterns and integrated therapeutic interfaces, as illustrated in Fig. 5.

3.4 Ultrasound-Mediated Drug Delivery and Biological Barrier Modulation

Ultrasound can facilitate therapeutic delivery through several mechanistically distinct roles. First, it can transiently modulate biological barriers, such as the BBB, to increase permeability. Second, acoustic radiation force, streaming, and related mechanical effects can enhance convective or interstitial transport. Third, ultrasound can directly activate acoustically responsive carriers to trigger local payload release. Finally, when coupled with structured or wearable interfaces, acoustic input can be temporally programmed to regulate release rate and cumulative dose. These mechanisms differ in the variable directly controlled by ultrasound and in the degree of external control over therapeutic delivery.

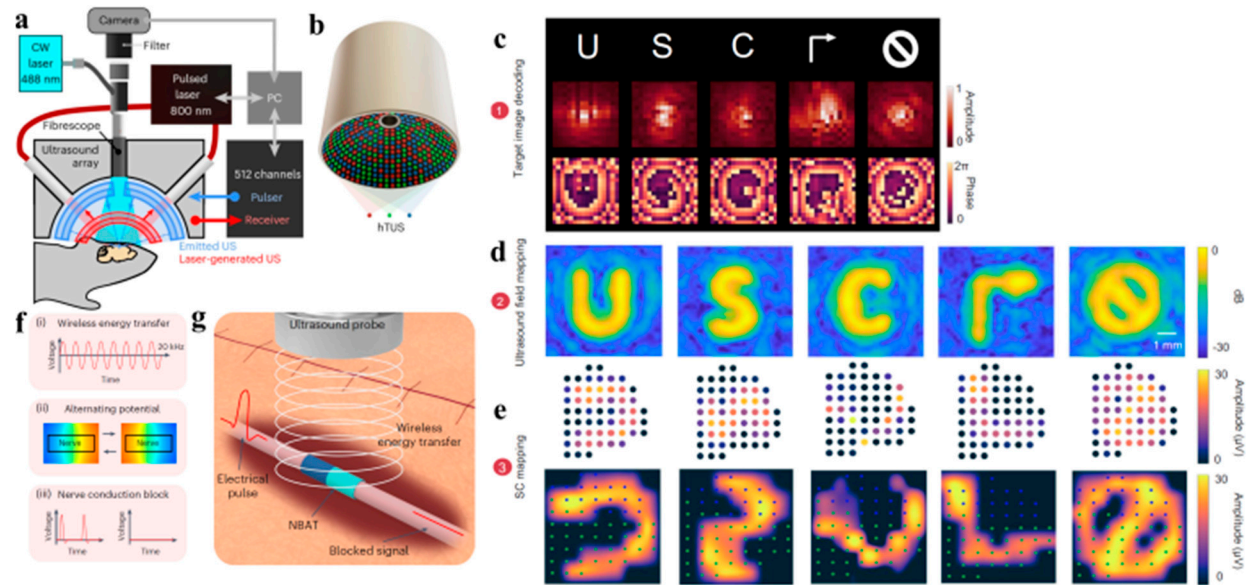


Figure 5: Emerging strategies for spatially precise and biointerface-assisted ultrasound neuromodulation. (a,b) Holographic transcranial ultrasound platform and 512-element matrix array for flexible field shaping. Reproduced with permission from Ref. [7]. Copyright © 2025, Hector Estrada et al. (c–e) Imaging-guided ultrasonic retinal stimulation, showing target-pattern encoding, experimentally generated two-dimensional acoustic patterns, and corresponding neuronal-response maps. Adapted from Ref. [47]. Copyright © 2024, Gengxi Lu et al. (f,g) Wireless bioresorbable triboelectric nerve-block system in which ultrasound-driven vibration is converted into an alternating electric field for peripheral nerve conduction block. Reproduced with permission from Ref. [48]. Copyright © 2026, Springer Nature.

3.4.1 Blood-Brain Barrier Opening

The BBB strongly restricts delivery of many biologics, nucleic acids, and nanomedicines. Transient BBB permeabilization can be induced by applying focused sonication in the presence of intravenously administered microbubbles [50]. Controlled bubble motion perturbs the vascular interface mechanically, whereas excessive cavitation increases the risk of endothelial and vascular injury [51–54].

Human studies have now moved beyond demonstrating reversible barrier opening toward testing whether the same approach can improve delivery of clinically relevant therapeutics [55–57]. Because safety depends on the bubble activity generated *in situ*, passive cavitation detection and feedback control can adjust acoustic pressure according to measured emissions rather than relying solely on preset transducer output [54,58,59]. Accordingly, focused-ultrasound-mediated BBB opening has progressed into clinical investigation, whereas many carrier-assisted gene-delivery and parenchymal-transport strategies remain predominantly preclinical.

Ultrasound-assisted CNS transport is also expanding beyond the vascular barrier. Focused-ultrasound-mediated BBB modulation can be combined with polymeric or lipid nanocarriers for spatially targeted non-viral gene delivery [60]. Beyond vascular delivery, low-intensity transcranial sonication can also facilitate movement of intrathecally administered agents from the CSF into brain parenchyma [61]. These findings broaden the concept of acoustic drug delivery from transient endothelial permeability to coordinated control of vascular, carrier-mediated, parenchymal, and CSF-associated transport pathways.

3.4.2 Sonoporation and Ultrasound-Responsive Carriers

Oscillating bubbles can impose brief mechanical perturbations on adjacent cell membranes, creating a reversible window that favors intracellular entry of therapeutic payloads [15,16,19]. An alternative strategy is to place acoustic sensitivity in the delivery vehicle rather than relying solely on tissue permeabilization.

Ultrasound-responsive liposomes provide a representative example of externally gated pharmacological release. Pulsed low-intensity ultrasound can trigger drug release after systemic or local carrier administration, enabling pharmacological action to be restricted to the sonicated region. Recent demonstrations include site-specific release of neuroactive agents and ultrasound-triggered local anesthetic delivery for peripheral nerve block [62]. Carrier size, monodispersity, shell elasticity, and colloidal stability remain important because they determine both acoustic responsiveness and biological distribution [63]. More broadly, ultrasound responsiveness is governed by the mechanical and interfacial properties of the carrier. Shell or matrix thickness and stiffness influence deformation and rupture thresholds, whereas carrier size and size distribution affect both acoustic interaction and biodistribution. Mechanical stability must be sufficient to prevent premature leakage while remaining compatible with acoustically triggered disruption or permeabilization. Payload–matrix interactions and colloidal stability further influence baseline retention and release kinetics. Therefore, carrier design and acoustic exposure should be considered as a coupled design problem rather than optimized independently.

3.4.3 Structured and Wearable Platforms for Programmable Transdermal Delivery

Structured transdermal delivery platforms can be broadly distinguished according to the degree of external control over drug transport. Passive systems rely primarily on diffusion, material dissolution, or degradation after application. Ultrasound-triggered systems introduce an externally applied acoustic stimulus to initiate or accelerate transport or payload release [64–66]. Programmable systems provide a further level of control, in which acoustic power, burst number, pulse timing, or treatment sequence can be deliberately adjusted to generate predefined temporal release profiles or cumulative doses. Importantly, programmable delivery remains open-loop unless physiological sensing automatically determines subsequent actuation [67–69].

An active acoustic metamaterial patch illustrates this principle: periodically arranged sharp microstructures can simultaneously interface with skin and reshape local pressure and streaming fields, while digital control of acoustic power and burst timing regulates release rate and cumulative dose [70]. Multi-burst epinephrine delivery in an anaphylaxis model further demonstrated that an already-applied patch can produce distinct temporal dosing profiles rather than a single predetermined administration [70]. More recently, spatiotemporal acoustic meta-patches have extended this concept by combining reconfigurable acoustic field shaping with impedance-matched microstructures, enabling coordinated control of localized heating, drug transport, and regenerative responses [71].

Wearable ultrasound-microneedle systems extend this concept by integrating conformable transducers, drug reservoirs, microneedles, and portable electronics [6,72,73]. These platforms establish an important distinction between passive and externally programmable drug delivery. Acoustic power, burst number, and treatment timing can be adjusted to regulate release profiles, but such systems remain open-loop unless physiological sensing automatically determines subsequent actuation. Closed-loop therapeutic ultrasound is discussed separately in Section 5.3.

Taken together, ultrasound-mediated drug delivery can be organized into four mechanistically distinct levels of control: (i) modulation of biological barriers; (ii) enhancement of convective or interstitial transport; (iii) acoustic activation of responsive carriers; and (iv) programmable release from structured or wearable

interfaces. These levels should not be conflated because they differ in both the controlled variable and the degree of therapeutic autonomy. Representative examples are summarized in Fig. 6. In contrast to clinically investigated BBB-opening approaches, most structured transdermal, microneedle-integrated, and wearable programmable delivery systems remain at the preclinical or proof-of-concept stage.

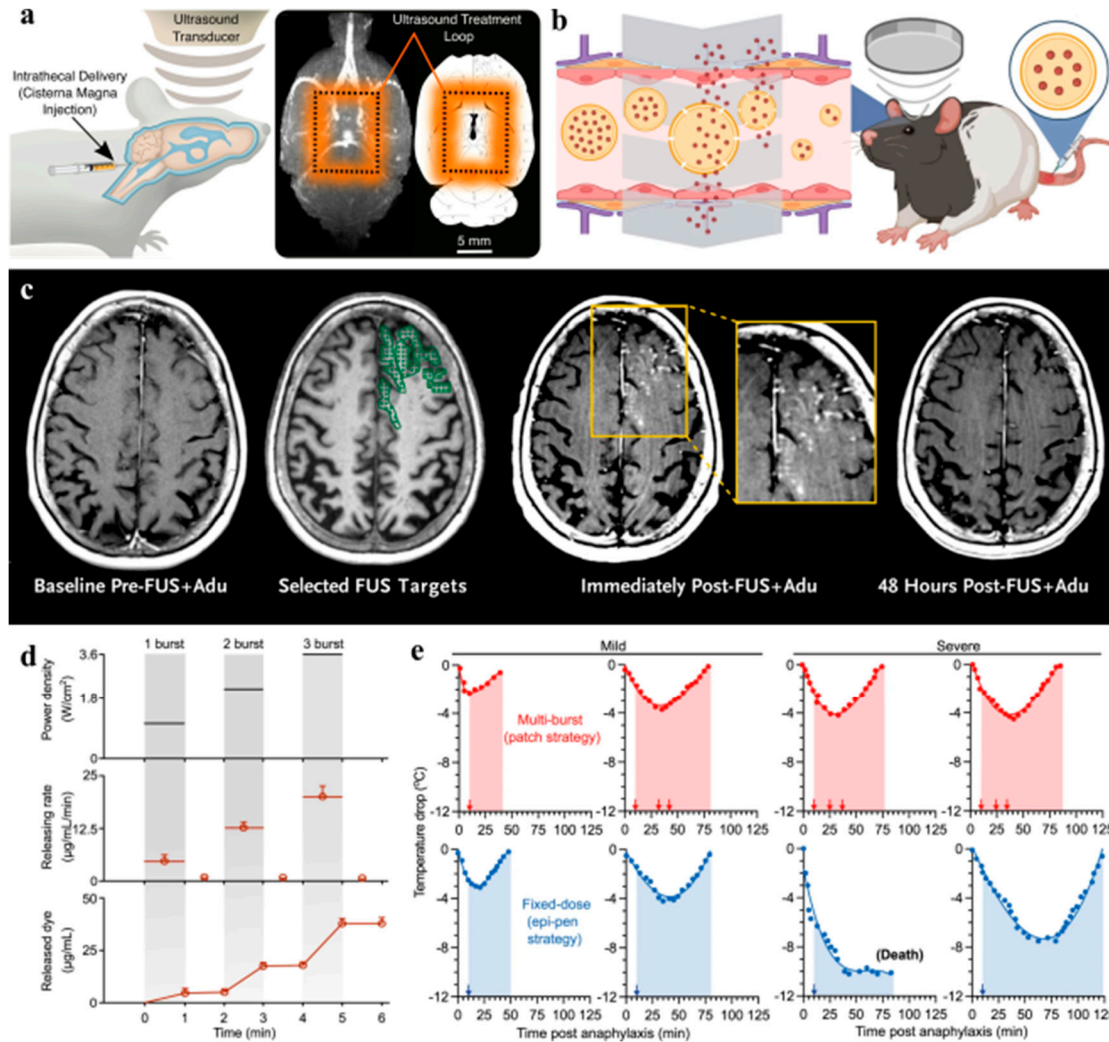


Figure 6: Ultrasound-mediated CNS transport and programmable drug delivery. (a) Ultrasound-enhanced CSF-associated transport after intrathecal administration. Reproduced with permission from Ref. [61]. Copyright © 2022, Elsevier. (b) Ultrasound-responsive carrier release. Reproduced with permission from Ref. [62]. Copyright © 2025, Mahaveer P. Purohit et al. (c) MRI-guided BBB opening and subsequent closure. Reproduced with permission from Ref. [57]. Copyright © 2024, Massachusetts Medical Society. (d) Burst-dependent control of transdermal drug release. (e) Multi-burst therapeutic rescue compared with fixed-dose injection, illustrating temporal control of treatment dose. (d,e) Reproduced with permission from Ref. [70]. Copyright © 2023, Junhua Xu et al.

4 Cross-Cutting Biological Responses and Combination Therapies

4.1 Immune Modulation

Immune modulation can arise downstream of several acoustic mechanisms and should not be treated as a separate acoustic modality. Thermal ablation can release tumor antigens and inflammatory mediators,

histotripsy can mechanically liberate intracellular material and danger signals, and ultrasound-mediated delivery can localize cytokines, checkpoint inhibitors, nucleic acids, or immunomodulatory nanoparticles [24,74–76].

Sonodynamic therapy represents a complementary combination strategy that can also intersect with antitumor immune modulation. Upon acoustic excitation, sonosensitizers promote the formation of reactive oxygen species, thereby imposing oxidative stress on tumor cells [77,78]. Emerging nanosonosensitizers incorporate catalytic materials, oxygen-regulating components, metal-organic frameworks, or piezoelectric elements to improve reactive-species generation and remodel the tumor microenvironment [79–82]. The resulting immune response nevertheless depends on the dominant physical interaction, treatment completeness, delivered therapeutic, tumor type, and baseline immune state.

4.2 Tissue Regeneration and Responsive Biointerfaces

At lower acoustic exposures, ultrasound may influence mechanotransduction, angiogenesis, extracellular-matrix remodeling, inflammatory signaling, and cell migration. Low-intensity pulsed ultrasound has long been investigated for bone and musculoskeletal regeneration, although benefit remains indication dependent and should not be generalized across regenerative settings [83–85]. A more recent direction combines ultrasound with responsive biomaterials. Ultrasound-mediated bioadhesion can transport anchoring species into wet tissue interfaces, while piezoelectric hydrogels, scaffolds, and aligned nanofiber conduits can convert transcutaneous ultrasound into localized electrical or mechanical stimulation for nerve, bone, cartilage, or wound repair [86–90]. These systems shift ultrasound from acting directly on tissue toward regulating a therapeutic biointerface with defined spatial and temporal behavior. Importantly, these biomaterials serve distinct functional roles within ultrasound-enabled therapeutic systems. Hydrogels may act as local drug reservoirs, acoustically responsive matrices, adhesive interfaces, or deformable sensing elements. Piezoelectric hydrogels and scaffolds can function as mechanoelectric transducers that convert ultrasound-induced deformation into localized electrical stimulation. Aligned nanofiber systems may simultaneously provide structural guidance for cell growth and ultrasound-mediated electromechanical cues for tissue regeneration. Thus, the therapeutic function of an ultrasound-responsive biomaterial depends not only on its composition but also on whether it is designed primarily for payload storage, acoustic transduction, mechanical interfacing, electrical conversion, or regenerative guidance.

5 Challenges and Perspectives

5.1 Quantitative Dosimetry, Safety, and Monitoring

A central translational challenge is the gap between device settings and the biological dose delivered at the target. Frequency, acoustic pressure, pulse duration, pulse repetition frequency, duty cycle, exposure duration, focal geometry, coupling conditions, anatomy, and exogenous acoustic agents all influence the *in situ* acoustic field. The relevant dose metric is modality specific: HIFU requires thermal-dose assessment; histotripsy requires characterization of cavitation activity and treatment margins; neuromodulation requires field localization while minimizing off-target stimulation and heating; and BBB opening generally aims to maintain controlled stable cavitation while avoiding damaging inertial cavitation and vascular injury [1,8,91,92].

Real-time monitoring therefore provides the connection between acoustic exposure and biological response. MR thermometry is appropriate for thermal intervention, whereas passive acoustic emissions, cavitation imaging, and feedback-controlled cavitation monitoring can guide bubble-mediated proce-

dures [12,52,93]. More broadly, the monitored variable should correspond to the dominant physical mechanism rather than rely on generic labels such as ‘low-intensity ultrasound’.

5.2 Patient-Specific Field Engineering and Device-Biointerface Co-Design

Anatomical variability remains a major obstacle to reproducible targeting. Skull thickness and density, rib geometry, tissue heterogeneity, motion, and coupling can substantially alter therapeutic fields. CT- and MRI-derived models can estimate transmission and phase aberration, while machine-learning methods may accelerate field prediction and aberration correction [10,94,95].

At the device level, phased arrays, acoustic holograms, metasurfaces, and structured biointerfaces provide increasingly sophisticated control of wavefront geometry and local transport. Holographic neuromodulation demonstrates how distributed pressure fields can recruit neural networks, whereas structured transdermal interfaces illustrate how field engineering can organize acoustic streaming for drug transport [7,49,70,96]. Across modalities, the acoustic source, field geometry, device-tissue interface, and biological target should therefore be co-designed rather than optimized independently. Wearable and biointegrated therapeutic ultrasound introduces additional interface-level challenges. Stable acoustic coupling must be maintained during motion and prolonged wear, because small changes in contact pressure, coupling-layer thickness, or interfacial air gaps can alter acoustic transmission. Device conformability must also be balanced against transducer efficiency and focal precision, particularly when rigid piezoelectric components are integrated with soft substrates. Long-term use further requires evaluation of material biocompatibility, thermal accumulation, mechanical durability, and tissue response. Finally, integrating sensing, therapeutic actuation, and control electronics within a compact wearable platform creates challenges in calibration and reproducibility, as therapeutic output may vary with device placement, anatomy, and repeated use. These considerations reinforce the need for co-design of the acoustic source, coupling interface, device mechanics, sensing modules, and biological target.

5.3 Toward Disease-Adaptive and Closed-Loop Therapeutic Ultrasound

Open-loop treatment applies predefined acoustic parameters or treatment sequences without using physiological feedback to modify subsequent actuation. Programmable systems allow acoustic parameters, spatial patterns, or temporal dosing schedules to be externally specified or updated, but the treatment remains operator- or program-driven. Disease-adaptive systems select or update treatment profiles according to a known or intermittently measured disease state. In contrast, closed-loop systems automatically modify subsequent therapeutic actuation according to measured physiological, acoustic, or therapeutic feedback. Thus, programmability and adaptation should not be considered synonymous with closed-loop control. The components required for such systems are now emerging across sensing and therapy. MR thermometry can guide adaptive thermal sonication, cavitation emissions can regulate BBB opening, bubble-cloud imaging can inform histotripsy, and neural recordings or functional imaging can provide target-engagement signals for neuromodulation [7,12,30,52]. Ultrasound is also becoming a readout modality: injectable bioresorbable metastructured hydrogels can encode intracranial pressure, temperature, pH, or flow as shifts in the reflected-ultrasound spectrum, while acoustically readable glucose-responsive microneedle patches can translate hydrogel swelling into an imaging signal for continuous glucose monitoring [97,98]. On the actuation side, intelligent acoustofluidic patches can couple physiological monitoring and machine-learning classification to automatic drug delivery, illustrating how ultrasound-enabled sensing and therapy may converge within a single feedback architecture [99,100].

A general closed-loop architecture can therefore be summarized as a sequence of disease sensing, state classification, acoustic actuation, controlled bioeffect or drug release, response monitoring, and subsequent dose adaptation, as illustrated in Fig. 7. The value of this framework is that it separates true feedback control from merely programmable treatment and provides a common language for comparing otherwise diverse therapeutic devices.

Artificial intelligence may assist state classification, patient-specific planning, aberration correction, target selection, and adaptive decision making, but algorithmic control should remain constrained by experimentally validated acoustic and biological safety limits [91,94]. The central challenge is therefore not simply to add sensors or computation to an ultrasound device, but to establish quantitative relationships among measured physiological state, acoustic input, local physical interaction, therapeutic response, and the control action applied on the next cycle.

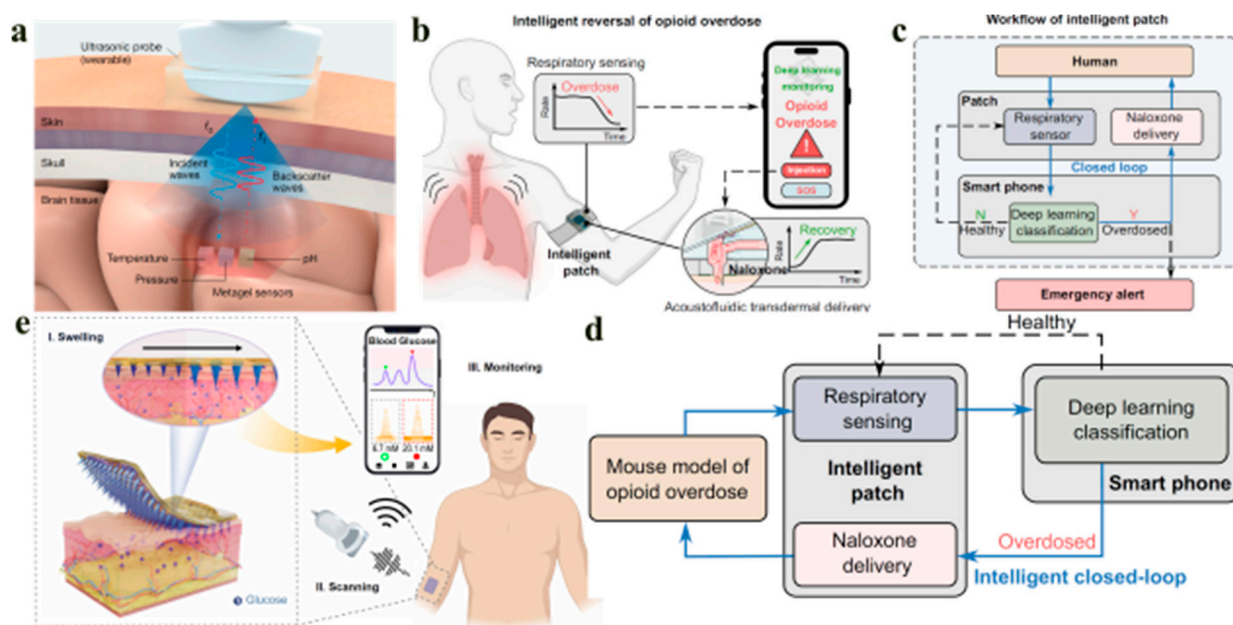


Figure 7: Toward intelligent, wearable, and closed-loop therapeutic ultrasound. (a) Injectable bioresorbable metas-structured hydrogel sensor for wireless ultrasonic monitoring of intracranial signals. Reproduced with permission from Ref. [98]. Copyright © 2024, Springer. (b–d) Wearable acoustofluidic system for opioid-overdose rescue, showing respiratory sensing, deep-learning-based overdose classification, automatic naloxone delivery, and the corresponding closed-loop treatment workflow. Reproduced with permission from Ref. [100]. Copyright © 2026, Yantao Xing et al. (e) Acoustically readable microneedle patch for continuous glucose monitoring. Reproduced with permission from Ref. [97] under the terms of the Creative Commons Attribution 4.0 International License.

6 Conclusion

Therapeutic ultrasound encompasses a spectrum of interventions ranging from irreversible thermal ablation and cavitation-driven mechanical fractionation to reversible neuromodulation and controlled therapeutic transport. Despite their diversity, these modalities share a common principle: acoustic parameters and field geometry determine the dominant local physical interaction, and that interaction determines the biological outcome.

Recent advances extend this framework beyond focal energy deposition. Holographic and patterned stimulation enable spatial control of neural recruitment, ultrasound-responsive carriers and structured

interfaces permit localized or temporally programmed pharmacology, and ultrasound-readable sensors create new opportunities to couple physiological monitoring directly to therapeutic actuation. These developments shift the field from treating ultrasound as a one-way energy source toward using it as a component of integrated sensing-and-actuation systems.

The evolution of therapeutic ultrasound can therefore be conceptualized as a progression from acoustic energy deposition and bioeffect control toward spatial field engineering, therapeutic transport, physiological sensing, temporal programming, disease-adaptive intervention, and ultimately closed-loop therapy.

Future progress will require closer integration of acoustic physics with responsive biomaterials, controlled drug delivery, wearable biointerfaces, biosensing, imaging, and adaptive control. Such convergence may allow ultrasound to evolve from a one-way source of therapeutic energy into an integrated platform that can sense biological state, deliver a defined physical or pharmacological intervention, monitor the resulting response, and adjust subsequent treatment. The defining capability of next-generation therapeutic ultrasound may therefore not be stronger acoustic output, but the ability to deliver the appropriate physical interaction at the appropriate location and time, while adapting therapy within a quantitatively validated safety window.

Acknowledgement: We gratefully acknowledge the support from the National Natural Science Foundation of China.

Funding Statement: This research was supported by the National Natural Science Foundation of China (32401201).

Author Contributions: Conceptualization, Yile Fang and Zhuhao Wu; literature investigation, Kaidi Ren and Zhenyu Cao; writing—original draft, Kaidi Ren and Zhenyu Cao; visualization, Kaidi Ren and Zhenyu Cao; writing—review and editing, Yile Fang and Zhuhao Wu; supervision, Yile Fang and Zhuhao Wu. All authors reviewed and approved the final version of the manuscript.

Availability of Data and Materials: Not applicable.

Ethics Approval: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. O'Reilly MA. Exploiting the mechanical effects of ultrasound for noninvasive therapy. *Science*. 2024;385(6714):eadp7206. [\[CrossRef\]](#).
2. Legon W, Strohman A. Low-intensity focused ultrasound for human neuromodulation. *Nat Rev Methods Prim*. 2024;4:91. [\[CrossRef\]](#).
3. Martínez-Fernández R. Focused ultrasound brain therapy is a new tool in the box. *Nat Rev Neurol*. 2024;20(8):443–4. [\[CrossRef\]](#).
4. Elias WJ, Lipsman N, Ondo WG, Ghanouni P, Kim YG, Lee W, et al. A randomized trial of focused ultrasound thalamotomy for essential tremor. *N Engl J Med*. 2016;375(8):730–9. [\[CrossRef\]](#).
5. Meng Y, Hynynen K, Lipsman N. Applications of focused ultrasound in the brain: from thermoablation to drug delivery. *Nat Rev Neurol*. 2021;17(1):7–22. [\[CrossRef\]](#).
6. Chen S, Ouyang Q, Miao X, Zhang F, Chen Z, Qian X, et al. Wearable ultrasound devices for therapeutic applications. *Nano Micro Lett*. 2025;18(1):45. [\[CrossRef\]](#).
7. Estrada H, Chen Y, Lemaire T, Davoudi N, Özbek A, Parduzi Q, et al. Holographic transcranial ultrasound neuromodulation enhances stimulation efficacy by cooperatively recruiting distributed brain circuits. *Nat Biomed Eng*. 2026;10(1):6–15. [\[CrossRef\]](#).
8. Bader KB, Padilla F, Haworth KJ, Ellens N, Dalecki D, Miller DL, et al. Overview of therapeutic ultrasound applications and safety considerations: 2024 update. *J Ultrasound Med*. 2025;44(3):381–433. [\[CrossRef\]](#).

9. Izadifar Z, Izadifar Z, Chapman D, Babyn P. An introduction to high intensity focused ultrasound: systematic review on principles, devices, and clinical applications. *J Clin Med*. 2020;9(2):460. [[CrossRef](#)].
10. Leung SA, Webb TD, Bitton RR, Ghanouni P, Butts Pauly K. A rapid beam simulation framework for transcranial focused ultrasound. *Sci Rep*. 2019;9:7965. [[CrossRef](#)].
11. Kennedy JE. High-intensity focused ultrasound in the treatment of solid tumours. *Nat Rev Cancer*. 2005;5(4):321–7. [[CrossRef](#)].
12. Vanne A, Hynynen K. MRI feedback temperature control for focused ultrasound surgery. *Phys Med Biol*. 2003;48(1):31–43. [[CrossRef](#)].
13. McGill KC, Baal JD, Bucknor MD. Update on musculoskeletal applications of magnetic resonance-guided focused ultrasound. *Skelet Radiol*. 2024;53(9):1869–77. [[CrossRef](#)].
14. Dalecki D. Mechanical bioeffects of ultrasound. *Annu Rev Biomed Eng*. 2004;6:229–48. [[CrossRef](#)].
15. Ohl CD, Arora M, Ikink R, de Jong N, Versluis M, Delius M, et al. Sonoporation from jetting cavitation bubbles. *Biophys J*. 2006;91(11):4285–95. [[CrossRef](#)].
16. Lentacker I, de Cock I, Deckers R, De Smedt SC, Moonen CTW. Understanding ultrasound induced sonoporation: definitions and underlying mechanisms. *Adv Drug Deliv Rev*. 2014;72:49–64. [[CrossRef](#)].
17. Bader KB, Vlaisavljevich E, Maxwell AD. For whom the bubble grows: physical principles of bubble nucleation and dynamics in histotripsy ultrasound therapy. *Ultrasound Med Biol*. 2019;45(5):1056–80. [[CrossRef](#)].
18. Nama N, Huang PH, Huang TJ, Costanzo F. Investigation of acoustic streaming patterns around oscillating sharp edges. *Lab Chip*. 2014;14(15):2824–36. [[CrossRef](#)].
19. Helfield B, Chen X, Watkins SC, Villanueva FS. Biophysical insight into mechanisms of sonoporation. *Proc Natl Acad Sci U S A*. 2016;113(36):9983–8. [[CrossRef](#)].
20. Recker F, Thudium M, Strunk H, Tonguc T, Dohmen S, Luechters G, et al. Multidisciplinary management to optimize outcome of ultrasound-guided high-intensity focused ultrasound (HIFU) in patients with uterine fibroids. *Sci Rep*. 2021;11(1):22768. [[CrossRef](#)].
21. Martínez-Fernández R, Máñez-Miró JU, Rodríguez-Rojas R, Del Álamo M, Shah BB, Hernández-Fernández F, et al. Randomized trial of focused ultrasound subthalamotomy for Parkinson's disease. *N Engl J Med*. 2020;383(26):2501–13. [[CrossRef](#)].
22. Krishna V, Fishman PS, Eisenberg HM, Kaplitt M, Baltuch G, Chang JW, et al. Trial of globus pallidus focused ultrasound ablation in Parkinson's disease. *N Engl J Med*. 2023;388(8):683–93. [[CrossRef](#)].
23. Lipsman N, Schwartz ML, Huang Y, Lee L, Sankar T, Chapman M, et al. MR-guided focused ultrasound thalamotomy for essential tremor: a proof-of-concept study. *Lancet Neurol*. 2013;12(5):462–8. [[CrossRef](#)].
24. Wei Z, Yu X, Huang M, Wen L, Lu C. Nanoplatfroms potentiated ablation-immune synergistic therapy through improving local control and suppressing recurrent metastasis. *Pharmaceutics*. 2023;15(5):1456. [[CrossRef](#)].
25. Cabras P, Auloge P, Bing F, Rao PP, Hoarau S, Dumont E, et al. A new versatile MR-guided high-intensity focused ultrasound (HIFU) device for the treatment of musculoskeletal tumors. *Sci Rep*. 2022;12(1):9095. [[CrossRef](#)].
26. Wu P, Lin W, Li KH, Lai HC, Lee MT, Tsai KW, et al. Focused ultrasound thalamotomy for the treatment of essential tremor: a 2-year outcome study of Chinese people. *Front Aging Neurosci*. 2021;13:697029. [[CrossRef](#)].
27. Williams RP, Simon JC, Khokhlova VA, Sapozhnikov OA, Khokhlova TD. The histotripsy spectrum: differences and similarities in techniques and instrumentation. *Int J Hyperth*. 2023;40:2233720. [[CrossRef](#)].
28. Maxwell AD, Wang TY, Cain CA, Fowlkes JB, Sapozhnikov OA, Bailey MR, et al. Cavitation clouds created by shock scattering from bubbles during histotripsy. *J Acoust Soc Am*. 2011;130(4):1888–98. [[CrossRef](#)].
29. Xu Z, Khokhlova TD, Cho CS, Khokhlova VA. Histotripsy: a method for mechanical tissue ablation with ultrasound. *Annu Rev Biomed Eng*. 2024;26(1):141–67. [[CrossRef](#)].
30. Mendiratta-Lala M, Wiggermann P, Pech M, Serres-Créixams X, White SB, Davis C, et al. The #HOPE4LIVER single-arm pivotal trial for histotripsy of primary and metastatic liver tumors. *Radiology*. 2024;312(3):e233051. [[CrossRef](#)].
31. Xu Z, Hall TL, Vlaisavljevich E, Lee FT Jr. Histotripsy: the first noninvasive, non-ionizing, non-thermal ablation technique based on ultrasound. *Int J Hyperth*. 2021;38(1):561–75. [[CrossRef](#)].

32. Hendricks-Wenger A, Weber P, Simon A, Saunier S, Coutermarsh-Ott S, Grider D, et al. Histotripsy for the treatment of cholangiocarcinoma liver tumors: *in vivo* feasibility and *ex vivo* dosimetry study. *IEEE Trans Ultrason Ferroelectr Freq Control*. 2021;68(9):2953–64. [[CrossRef](#)].
33. Lu N, Yeats EM, Sukovich JR, Hall TL, Pandey AS, Xu Z. Treatment envelope of transcranial histotripsy: challenges and strategies to maximize the treatment location profile. *Phys Med Biol*. 2024;69(22):225006. [[CrossRef](#)].
34. Folloni D, Verhagen L, Mars RB, Fouragnan E, Constans C, Aubry JF, et al. Manipulation of subcortical and deep cortical activity in the primate brain using transcranial focused ultrasound stimulation. *Neuron*. 2019;101(6):1109–16.e5. [[CrossRef](#)].
35. Zeng K, Darmani G, Fomenko A, Xia X, Tran S, Nankoo JF, et al. Induction of human motor cortex plasticity by theta burst transcranial ultrasound stimulation. *Ann Neurol*. 2022;91(2):238–52. [[CrossRef](#)].
36. Chou T, Deckersbach T, Guerin B, Sretavan Wong K, Borron BM, Kanabar A, et al. Transcranial focused ultrasound of the amygdala modulates fear network activation and connectivity. *Brain Stimul*. 2024;17(2):312–20. [[CrossRef](#)].
37. Shi Y, Cai G, Wu W. A panoramic review of transcranial focused ultrasound neuromodulation: from basic research to clinical applications. *J Neuroeng Rehabil*. 2025;22(1):227. [[CrossRef](#)].
38. Yaakub SN, White TA, Roberts J, Martin E, Verhagen L, Stagg CJ, et al. Transcranial focused ultrasound-mediated neurochemical and functional connectivity changes in deep cortical regions in humans. *Nat Commun*. 2023;14(1):5318. [[CrossRef](#)].
39. Fomenko A, Chen KS, Nankoo JF, Saravanamuttu J, Wang Y, El-Baba M, et al. Systematic examination of low-intensity ultrasound parameters on human motor cortex excitability and behavior. *eLife*. 2020;9:e54497. [[CrossRef](#)].
40. Tufail Y, Matyushov A, Baldwin N, Tauchmann ML, Georges J, Yoshihiro A, et al. Transcranial pulsed ultrasound stimulates intact brain circuits. *Neuron*. 2010;66(5):681–94. [[CrossRef](#)].
41. Legon W, Sato TF, Opitz A, Mueller J, Barbour A, Williams A, et al. Transcranial focused ultrasound modulates the activity of primary somatosensory cortex in humans. *Nat Neurosci*. 2014;17(2):322–9. [[CrossRef](#)].
42. Yoo S, Mittelstein DR, Hurt RC, Lacroix J, Shapiro MG. Focused ultrasound excites cortical neurons *via* mechanosensitive calcium accumulation and ion channel amplification. *Nat Commun*. 2022;13(1):493. [[CrossRef](#)].
43. Krasovitski B, Frenkel V, Shoham S, Kimmel E. Intramembrane cavitation as a unifying mechanism for ultrasound-induced bioeffects. *Proc Natl Acad Sci U S A*. 2011;108(8):3258–63. [[CrossRef](#)].
44. Plaksin M, Shoham S, Kimmel E. Intramembrane cavitation as a predictive bio-piezoelectric mechanism for ultrasonic brain stimulation. *Phys Rev X*. 2014;4:011004. [[CrossRef](#)].
45. Blackmore DG, Razansky D, Götz J. Ultrasound as a versatile tool for short- and long-term improvement and monitoring of brain function. *Neuron*. 2023;111(8):1174–90. [[CrossRef](#)].
46. Braun V, Blackmore J, Cleveland RO, Butler CR. Transcranial ultrasound stimulation in humans is associated with an auditory confound that can be effectively masked. *Brain Stimul*. 2020;13(6):1527–34. [[CrossRef](#)].
47. Lu G, Gong C, Sun Y, Qian X, Rajendran Nair DS, Li R, et al. Noninvasive imaging-guided ultrasonic neurostimulation with arbitrary 2D patterns and its application for high-quality vision restoration. *Nat Commun*. 2024;15:4481. [[CrossRef](#)].
48. Kim YJ, Kim SH, Park BJ, Jeon J, Kang D, Chung Y, et al. Wireless and bioresorbable triboelectric nerve block system for postoperative pain control. *Nat Biomed Eng*. 2026:1–12. [[CrossRef](#)].
49. Hu Z, Yang Y, Yang L, Gong Y, Chukwu C, Ye D, et al. Airy-beam holographic sonogenetics for advancing neuromodulation precision and flexibility. *Proc Natl Acad Sci U S A*. 2024;121(26):e2402200121. [[CrossRef](#)].
50. Gao J, Xia ZJ, Gunasekar S, Jiang C, Karp JM, Joshi N. Precision drug delivery to the central nervous system using engineered nanoparticles. *Nat Rev Mater*. 2024;9(8):567–88. [[CrossRef](#)].
51. Hynynen K, McDannold N, Vykhodtseva N, Jolesz FA. Noninvasive MR imaging-guided focal opening of the blood-brain barrier in rabbits. *Radiology*. 2001;220(3):640–6. [[CrossRef](#)].
52. O'Reilly MA, Hynynen K. Blood-brain barrier: real-time feedback-controlled focused ultrasound disruption by using an acoustic emissions-based controller. *Radiology*. 2012;263(1):96–106. [[CrossRef](#)].
53. Burgess MT, Apostolakis I, Konofagou EE. Power cavitation-guided blood-brain barrier opening with focused ultrasound and microbubbles. *Phys Med Biol*. 2018;63(6):065009. [[CrossRef](#)].

54. Bae S, Liu K, Pouliopoulos AN, Ji R, Jiménez-Gambín S, Yousefian O, et al. Transcranial blood-brain barrier opening in Alzheimer's disease patients using a portable focused ultrasound system with real-time 2-D cavitation mapping. *Theranostics*. 2024;14(11):4519–35. [[CrossRef](#)].
55. Meng Y, Reilly RM, Pezo RC, Trudeau M, Sahgal A, Singnurkar A, et al. MR-guided focused ultrasound enhances delivery of trastuzumab to Her2-positive brain metastases. *Sci Transl Med*. 2021;13(615):eabj4011. [[CrossRef](#)].
56. Sonabend AM, Gould A, Amidei C, Ward R, Schmidt KA, Zhang DY, et al. Repeated blood-brain barrier opening with an implantable ultrasound device for delivery of albumin-bound paclitaxel in patients with recurrent glioblastoma: a phase 1 trial. *Lancet Oncol*. 2023;24(5):509–22. [[CrossRef](#)].
57. Rezai AR, D'Haese PF, Finomore V, Carpenter J, Ranjan M, Wilhelmsen K, et al. Ultrasound blood-brain barrier opening and aducanumab in Alzheimer's disease. *N Engl J Med*. 2024;390(1):55–62. [[CrossRef](#)].
58. Carpentier A, Canney M, Vignot A, Reina V, Beccaria K, Horodyckid C, et al. Clinical trial of blood-brain barrier disruption by pulsed ultrasound. *Sci Transl Med*. 2016;8(343):343re2. [[CrossRef](#)].
59. Lipsman N, Meng Y, Bethune AJ, Huang Y, Lam B, Masellis M, et al. Blood-brain barrier opening in Alzheimer's disease using MR-guided focused ultrasound. *Nat Commun*. 2018;9(1):2336. [[CrossRef](#)].
60. Gordon EN, Debski AC, Breza VR, Hoch MR, Anwar NZ, Imomnazarov K, et al. Focused ultrasound is poised to take non-viral gene therapies to the blood-brain barrier—And beyond. *Cell Biomater*. 2026;2(9):100461. [[CrossRef](#)].
61. Aryal M, Azadian MM, Hart AR, Macedo N, Zhou Q, Rosenthal EL, et al. Noninvasive ultrasonic induction of cerebrospinal fluid flow enhances intrathecal drug delivery. *J Control Release*. 2022;349:434–42. [[CrossRef](#)].
62. Purohit MP, Yu BJ, Roy KS, Xiang Y, Ewbank SN, Azadian MM, et al. Acoustically activatable liposomes as a translational nanotechnology for site-targeted drug delivery and noninvasive neuromodulation. *Nat Nanotechnol*. 2025;20(11):1688–99. [[CrossRef](#)].
63. van Elburg B, Deprez J, van den Broek M, De Smedt SC, Versluis M, Lajoinie G, et al. Dependence of sonoporation efficiency on microbubble size: an *in vitro* monodisperse microbubble study. *J Control Release*. 2023;363:747–55. [[CrossRef](#)].
64. Wang X, Han C, Xia J, Cui C, Min P, Meng X, et al. Ultrasound-mediated piezoelectric microneedles regulating macrophage polarization and remodeling pathological microenvironment for lymphedema improvement. *ACS Nano*. 2025;19(1):1447–62. [[CrossRef](#)].
65. Gao J, Zheng Y, Chen W, Liu J, Huang G, Li Y, et al. A wearable ultrasound-assisted microneedle system for the treatment of poorly permeable skin lesions. *Acta Biomater*. 2026;218:214–29. [[CrossRef](#)].
66. Azagury A, Khoury L, Enden G, Kost J. Ultrasound mediated transdermal drug delivery. *Adv Drug Deliv Rev*. 2014;72:127–43. [[CrossRef](#)].
67. Mitragotri S, Blankschtein D, Langer R. Ultrasound-mediated transdermal protein delivery. *Science*. 1995;269(5225):850–3. [[CrossRef](#)].
68. Wu Q, Pan C, Shi P, Zou L, Huang S, Zhang N, et al. On-demand transdermal drug delivery platform based on wearable acoustic microneedle array. *Chem Eng J*. 2023;477:147124. [[CrossRef](#)].
69. Park D, Park H, Seo J, Lee S. Sonophoresis in transdermal drug deliverys. *Ultrasonics*. 2014;54(1):56–65. [[CrossRef](#)].
70. Xu J, Cai H, Wu Z, Li X, Tian C, Ao Z, et al. Acoustic metamaterials-driven transdermal drug delivery for rapid and on-demand management of acute disease. *Nat Commun*. 2023;14:869. [[CrossRef](#)].
71. Wu Z, Gan J, Zhao Y. Spatiotemporal acoustic meta-patches for multifactorial wound treatment. *Bioact Mater*. 2026;60:191–202. [[CrossRef](#)].
72. Zhang S, Zhou Z, Chen L, Zeng YJ, Xu T. Wearable ultrasound microneedle patch for on-demand and sustained management of gouty arthritis. *npj Flex Electron*. 2026;10:53. [[CrossRef](#)].
73. Chen X, Niu Y, Zheng C, Zhao K, Cai Z, Luo Z, et al. Design and evaluation of a pump-free ultrasonic atomization-driven hollow microneedle array for transdermal drug delivery. *Int J Pharm*. 2026;701:127152. [[CrossRef](#)].
74. Xue L, Thatté AS, Mai D, Haley RM, Gong N, Han X, et al. Responsive biomaterials: optimizing control of cancer immunotherapy. *Nat Rev Mater*. 2024;9(2):100–18. [[CrossRef](#)].
75. Hendricks-Wenger A, Hutchison R, Vlasisavljevich E, Allen IC. Immunological effects of histotripsy for cancer therapy. *Front Oncol*. 2021;11:681629. [[CrossRef](#)].
76. Xue H, Jin J, Huang X, Tan Z, Zeng Y, Lu G, et al. Wearable flexible ultrasound microneedle patch for cancer immunotherapy. *Nat Commun*. 2025;16:2650. [[CrossRef](#)].

77. Rosenthal I, Sostaric JZ, Riesz P. Sonodynamic therapy—a review of the synergistic effects of drugs and ultrasound. *Ultrason Sonochem.* 2004;11(6):349–63. [[CrossRef](#)].
78. Pan X, Wang H, Wang S, Sun X, Wang L, Wang W, et al. Sonodynamic therapy (SDT): a novel strategy for cancer nanotheranostics. *Sci China Life Sci.* 2018;61(4):415–26. [[CrossRef](#)].
79. Zhu P, Chen Y, Shi J. Nanoenzyme-augmented cancer sonodynamic therapy by catalytic tumor oxygenation. *ACS Nano.* 2018;12(4):3780–95. [[CrossRef](#)].
80. Yang F, Dong J, Li Z, Wang Z. Metal-organic frameworks (MOF)-assisted sonodynamic therapy in anticancer applications. *ACS Nano.* 2023;17(5):4102–33. [[CrossRef](#)].
81. Jiang Z, Xiao W, Fu Q. Stimuli responsive nanosonosensitizers for sonodynamic therapy. *J Control Release.* 2023;361:547–67. [[CrossRef](#)].
82. Pu Y, Zhou B, Bing J, Wang L, Chen M, Shen Y, et al. Ultrasound-triggered and glycosylation inhibition-enhanced tumor piezocatalytic immunotherapy. *Nat Commun.* 2024;15:9023. [[CrossRef](#)].
83. Jw B, Bhandari M, Ta E, Schemitsch E, Jd H, Tornetta P. Re-evaluation of low intensity pulsed ultrasound in treatment of tibial fractures (TRUST): randomized clinical trial. *BMJ Br Med J.* 2016;355:i5351. [[CrossRef](#)].
84. Melde K, Athanassiadis AG, Missirlis D, Shi M, Seneca S, Fischer P. Ultrasound-assisted tissue engineering. *Nat Rev Bioeng.* 2024;2(6):486–500. [[CrossRef](#)].
85. Heckman JD, Ryaby JP, McCabe J, Frey JJ, Kilcoyne RF. Acceleration of tibial fracture-healing by non-invasive, low-intensity pulsed ultrasound. *J Bone Joint Surg Am.* 1994;76(1):26–34. [[CrossRef](#)].
86. Ma Z, Bourquard C, Gao Q, Jiang S, De Iure-Grimmel T, Huo R, et al. Controlled tough bioadhesion mediated by ultrasound. *Science.* 2022;377(6607):751–5. [[CrossRef](#)].
87. Xu D, Fu S, Zhang H, Lu W, Xie J, Li J, et al. Ultrasound-responsive aligned piezoelectric nanofibers derived hydrogel conduits for peripheral nerve regeneration. *Adv Mater.* 2024;36(28):e2307896. [[CrossRef](#)].
88. Zhang F, Lv M, Wang S, Li M, Wang Y, Hu C, et al. Ultrasound-triggered biomimetic ultrashort peptide nanofiber hydrogels promote bone regeneration by modulating macrophage and the osteogenic immune microenvironment. *Bioact Mater.* 2024;31:231–46. [[CrossRef](#)].
89. Wu S, Zhang H, Wang S, Sun J, Hu Y, Liu H, et al. Ultrasound-triggered *in situ* gelation with ROS-controlled drug release for cartilage repair. *Mater Horiz.* 2023;10(9):3507–22. [[CrossRef](#)].
90. Wang F, Qiu J, Guan S, Chen S, Nie X, Fu Z, et al. An ultrasound-responsive hydrogel with piezoelectric-enhanced electrokinetic effect accelerates neurovascular regeneration for diabetic wound healing. *Mater Today.* 2025;84:48–64. [[CrossRef](#)].
91. Aubry JF, Attali D, Schafer ME, Fouragnan E, Caskey CF, Chen R, et al. ITRUSST consensus on biophysical safety for transcranial ultrasound stimulation. *Brain Stimul.* 2025;18(6):1896–905. [[CrossRef](#)].
92. Sapareto SA, Dewey WC. Thermal dose determination in cancer therapy. *Int J Radiat Oncol.* 1984;10(6):787–800. [[CrossRef](#)].
93. Chien CY, Yang Y, Gong Y, Yue Y, Chen H. Blood-brain barrier opening by individualized closed-loop feedback control of focused ultrasound. *BME Front.* 2022;2022:9867230. [[CrossRef](#)].
94. Naftchi-Ardebili K, Singh K, Popelka GR, Pauly KB. A deep-learning model for one-shot transcranial ultrasound simulation and phase aberration correction. *Med Phys.* 2026;53(1):e70259. [[CrossRef](#)].
95. Zhang Q, Sun W, Deng J, Qi T, Wan M, Lu M. Transcranial adaptive aberration correction using deep learning for phased-array ultrasound therapy. *Ultrasonics.* 2025;152:107641. [[CrossRef](#)].
96. Wang C, Chen X, Wang L, Makihata M, Liu HC, Zhou T, et al. Bioadhesive ultrasound for long-term continuous imaging of diverse organs. *Science.* 2022;377(6605):517–23. [[CrossRef](#)].
97. Zhang W, Xu J, Li X, Jang Y, Liu Q, Ma W, et al. Augmenting ultrasound for continuous glucose monitoring *via* a wearable acoustically readable microneedle patch. *Sci Adv.* 2026;12(18):eaec3209. [[CrossRef](#)].
98. Tang H, Yang Y, Liu Z, Li W, Zhang Y, Huang Y, et al. Injectable ultrasonic sensor for wireless monitoring of intracranial signals. *Nature.* 2024;630(8015):84–90. [[CrossRef](#)].
99. Hu H, Huang H, Li M, Gao X, Yin L, Qi R, et al. A wearable cardiac ultrasound imager. *Nature.* 2023;613(7945):667–75. [[CrossRef](#)].
100. Xing Y, Yang Y, Li X, Cai H, Wu Z, Ao Z, et al. A wearable acoustofluidic patch for rapid reversal of opioid overdose. *Nat Commun.* 2026;17(1):10092. [[CrossRef](#)].