Current Neurology and Neuroscience Reports (2022) 22:197–208
https://doi.org/10.1007/s11910-022-01185-8

MOVEMENT DISORDERS (T. SIMUNI, SECTION EDITOR)

Essential Tremor—Do We Have Better Therapeutics? A Review of Recent Advances and Future Directions

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Accepted: 18 January 2022 / Published online: 2 March 2022

Abstract

Purpose of Review Essential tremor (ET) is a very common condition that significantly impacts quality of life. Current medical treatments are quite limited, and while surgical treatments like deep brain stimulation (DBS) can be very effective, they come with their own limitations as well as procedural risks. This article reviews updates on recent advances and future directions in the treatment of ET.

Recent Findings A new generation of pharmacologic agents specifically designed for ET is in clinical trials. Advances in DBS technology continue to improve this therapy. MRI-guided focused ultrasound (MRgFUS) is now an approved noninvasive ablative treatment for ET that is effective and shows potential for continuing improvement. The first peripheral stimulation device for ET has also now been approved.

Summary This article reviews updates on the treatment of ET, encompassing pharmacologic agents in clinical trials, DBS, MRgFUS, and noninvasive stimulation therapies. Recent treatment advances and future directions of development show a great deal of promise for ET therapeutics.

Keywords Essential tremor · Treatment · Clinical trials · Deep brain stimulation · MRI-guided focused ultrasound

Introduction

Essential tremor (ET) is a remarkably common condition with prevalence estimates that conservatively range from 0.9 to 5% of the population [1, 2]. It may be the most common adult movement disorder and is certainly the most common tremor syndrome. ET is a slowly progressive condition with age of onset encompassing the lifespan [3]. It is characterized by rhythmic oscillatory movement (tremor) involving hands, head, voice, and/or rarely legs [4]. Although the majority of people with ET do not seek medical attention [5], ET has nonetheless been shown to have a negative impact on quality of life and daily activities for most patients and for many is severe enough to be disabling [6–8].

Despite the prevalence and potentially disabling nature of symptoms, currently available pharmacologic treatment is very limited and is devoid of any medications specifically designed for ET. Surgical treatments can be quite efficacious though have inherent procedural risks that often limit their utilization. This article reviews updates in the treatment of ET, categorized into pharmacologic therapy, deep brain stimulation, ablative therapies (with special focus on MRI-guided focused ultrasound), and noninvasive stimulation therapies. Recent advances and new directions (including ongoing clinical trials) will be highlighted.

Pharmacologic Therapy

Established Medications

Despite how prevalent ET is, the symptomatic medication arsenal consists exclusively of repurposed drugs, and there have been no new drugs approved for ET in more than three decades. As suggested by evidence-based guidelines, the first-line therapies for ET are propranolol (non-selective β-adrenergic blocker) and primidone

Topical Collection on *Movement Disorders*

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(barbiturate anticonvulsant) [9, 10••]. Only 30–70% of patients respond to first-line therapies with a 50–60% average tremor reduction and sustained benefits for at least a year in about 85% of responders [11, 12]. However, even fewer receive meaningful functional improvement. There are additionally a number of second- and third-line medications with less evidence for efficacy that are commonly used as monotherapy or adjunctive treatments, such as topiramate, gabapentin, and mirtazapine among others [10••]. The less than ideal efficacy (particularly in cases of more severe tremor) and dose-limiting adverse effects of currently available medications are not surprising given the lack of ET specificity in the mechanisms of these drugs.

Investigational Medications

In light of the limitations of current pharmacologic treatments, drug development programs are underway (Table 1) with the goal of establishing the first effective medications specifically designed for ET.

Pathophysiologic Basis

While the precise etiology of ET remains largely unknown, abnormal neuronal oscillatory activity in wide-spanning networks involved in motor control has been implicated in the pathophysiology of ET for some time [13]. In recent years, studies of the olivo-cerebello-thalamo-cortical pathways

Table 1 Key ongoing and future clinical trials of pharmacologic therapies in ET

Medication class	Sponsor	Drug	Phase	Description	Estimated enrollment	Status	Estimated primary outcome completion date*	National Clinical Trial number
TTCC antagonist	Jazz Pharmaceuticals	JZP385	2b	Efficacy and safety study with multiple doses. R/DB/PC	400 (multi-center)	Recruiting	Nov 2023	NCT05122650
	Praxis Precision Medicines	PRAX-944	2a	Efficacy, safety, tolerability, and pharmacokinetics study. Open-label low dose and dose titration, then high dose R/DB/PC	24 (multi-center)	Recruiting	Dec 2021	NCT05021978
	Praxis Precision Medicines	PRAX-944	2b	Efficacy and safety study with multiple doses. R/DB/PC	112 (multi-center)	Recruiting	Sept 2022	NCT05021991
	Neurocrine Biosciences	NBI-827104	2	Efficacy, safety, tolerability, and pharmacokinetics study. R/DB/PC, crossover design	28 (single center)	Recruiting	March 2022	NCT04880616
GABA-A receptor PAM	Praxis Precision Medicines	PRAX-114	2			Planning		
	Sage Therapeutics	SAGE-324	2b	Dose optimization		Planning		
SK channel PAM	Cadent Therapeutics	CAD-1883	2b			Unknown		

ET essential tremor, *TTCC* T-type calcium channel, *R/DB/PC* randomized/double-blind/placebo-controlled, *GABA* gamma aminobutyric acid, *PAM* positive allosteric modulator, *SK channel* small-conductance calcium-activated potassium channel

*As per clinicaltrials.gov listing

have made significant strides toward establishing a clearer pathophysiologic model. This circuit's inherent potential for automaticity, synchrony, and signal amplification may set the stage for development of excessive rhythmicity and consequently tremor [14–18]. Within this circuitry, T-type calcium channels (TTCC) appear to play a key role in amplification of rhythmicity at multiple levels [19–21]. On the other hand, GABAergic (GABA-A in particular) transmission appears to play a role in curbing generation and propagation of excessive rhythmicity at multiple levels [22–25]. Aberrancies that result in either overactive promoters of rhythmicity or underactive inhibitors of rhythmicity may lead to development of tremor.

These principles are drawn from and consistent with studies of ET mouse models and humans with ET. Harmaline-treated mice are commonly used ET disease models that develop action tremor and excessive cerebellar rhythmicity at least in part due to their increased TTCC activity and decreased GABAergic activity [14]. Mice lacking specific TTCC genes have actually been shown to be resistant to harmaline-induced cerebellar oscillations and tremor [26]. From the GABA perspective, humans with ET may have reduced cerebellar GABAergic transmission, impairment in GABAergic Purkinje cells, and decreased numbers of deep cerebellar nuclei GABA receptors [22, 27–29]. GABA-A receptor knockout mice manifest postural and kinetic tremor and thus are also commonly used as ET disease models [30]. In preclinical studies, compounds with TTCC antagonist properties have improved tremor in both harmaline and GABA-A receptor knockout ET models [31].

T-Type Calcium Channel Antagonists

TTCCs are a logical target for antagonism in novel ET therapeutics given their role in amplifying rhythmicity in tremor-producing networks and the finding of increased activity of these channels in ET. The following are selective TTCC antagonists in clinical trials.

JZP385 (formerly known as CX-8998) (Cavion, Charlottesville, VA; Jazz Pharmaceuticals, Dublin, Ireland) was studied in a phase 2 randomized, placebo-controlled trial (T-CALM) that did not meet its primary endpoint of an improved independent video-rated tremor scale [32]. However, blinded in-person clinician rating of this scale and blinded participant rating of an ADL scale both showed improvements compared to placebo. Dizziness was the most common adverse event and dropout rate due to adverse events was 17%. A phase 2b study is underway.

PRAX-944 (Praxis Precision Medicines, Cambridge, MA) has had reportedly favorable phase 1 safety data [33]. A phase 2a study is underway, and a phase 2b study has begun recruiting.

NBI-827104 (Neurocrine Biosciences, San Diego, CA) has also had reportedly favorable phase 1 safety data [34], and a phase 2 study in ET is underway.

GABA-A Receptor Positive Allosteric Modulators

GABA-A receptors have long been a putative therapeutic target for ET, extrapolated initially from beneficial symptomatic effects of alcohol but established further in newer pathophysiologic models. Given their role in inhibiting excessive rhythmicity in tremor-producing networks and the findings of reduced GABAergic activity in ET, GABA-A receptors remain a logical therapeutic target. The following are GABA-A receptor positive allosteric modulators currently in clinical trials.

Sage Therapeutics (Cambridge, MA) and Biogen (Cambridge, MA) have developed SAGE-324, which is currently under study for ET. Topline results of a phase 2 trial (KINETIC) have been released, reporting reduction in upper limb tremor by 36% on average with higher efficacy in more severe tremor [35]. However, they also reported adverse effects of somnolence in 62% and dizziness in 38%, resulting in dose reductions in the majority of participants as well as a 38% dropout rate. A phase 2b study is being planned for dose optimization.

Praxis Precision Medicines is also studying a compound PRAX-114 in this class. PRAX-114 has primarily been under study for psychiatric indications, but has had reportedly favorable preliminary safety data, and a phase 2 study of this compound is planned for ET as well [33].

SK Channel Positive Allosteric Modulators

Small-conductance calcium-activated potassium (SK) channels are involved in neuronal repolarization and may attenuate somatic hyperexcitability [36]. SK channels have expression in Purkinje cells and are a potential therapeutic target for modulating excessive cerebellar rhythmicity [37]. CAD-1883 (Cadent Therapeutics, Cambridge, MA) is an SK channel positive allosteric modulator. An open-label phase 2a study (Cadence-1) was completed with reportedly favorable safety data and improvements in blinded tremor scores and kinematic sensor outcomes [38]. Cadent Therapeutics has since been acquired by Novartis (Basel, Switzerland) [39]. Further studies with this compound are still planned although the current status is unclear.

Deep Brain Stimulation

Deep brain stimulation (DBS) of the ventral intermediate (VIM) nucleus of the thalamus is a well-established second-line therapy for ET, and although thalamotomy

was the original surgical ET treatment (see the "Ablative Therapies": "Radiofrequency" section), DBS is now the preferred surgical treatment for patients with medication-refractory tremor [10••]. In the only randomized trial comparing VIM DBS with traditional radiofrequency thalamotomy in patients with tremor, DBS resulted in greater functional improvement and less frequent adverse events [40, 41]. Serious adverse event rates for VIM DBS typically run in the single digit percentages and include intracranial hemorrhage and soft tissue infections [42•, 43]. The adverse event profile of DBS is otherwise generally mild but does include neurologic symptoms seen with thalamotomy such as dysarthria, gait ataxia, and paresthesias [44, 45]. These issues may be seen in 20–50% of patients with unilateral VIM DBS and 60–85% of those with bilateral VIM DBS, but the vast majority are stimulation-related and thus (unlike with thalamotomy) can usually be improved or resolved with adjustments in stimulation parameters (though potentially at the expense of tremor benefit) [42•, 43, 46–48]. Several case series of unilateral DBS in ET have confirmed improvement in various tremor and functional performance rating scales (generally around 50–60% improvement in overall tremor and 70–90% improvement in contralateral upper limb tremor) [10••, 11, 42•, 44, 48, 49].

Long-term studies of VIM DBS in ET have shown a significant degree of continued benefit even after 10 years [50]. However, such studies have also demonstrated that worsening of tremor over time (on average of > 50% worsening of tremor after 6 years) may occur in 10–40% of patients [11, 42•, 45, 48, 51–55]. Concurrently, a reliable escalation of DBS stimulation amplitude is required over time, which may encroach on the limits of therapeutic windows. When tremor worsening is thought to be due to a decline in the magnitude of DBS benefit as opposed to disease progression, it is termed "habituation." While there is not full consensus on the concept of habituation, a few recent studies have more convincingly differentiated habituation from ET disease progression and surgical- or programming-related factors [56•, 57, 58]; one such study estimated habituation may account for 13% of overall tremor worsening over time [56•].

Recent Advances

Although DBS is a relatively safe and highly effective treatment for ET with good long-term benefits for most patients, habituation and restricted therapeutic windows due to stimulation-related adverse effects are two primary limitations of this therapy that many patients experience. Recent advances and future directions in DBS show promise in improving the therapy further.

Directional Stimulation

Directional stimulation refers to segmentation of DBS electrode contacts in the axial plane coupled with independent current control of these segments. This enables current steering in the axial plane to allow more precise targeting of benefit structures and avoidance of side effect structures. Preliminary studies have shown that directional stimulation allows for benefit at lower stimulation amplitudes, increases therapeutic windows, and allows for more efficient energy usage when compared to nondirectional stimulation [59••]. Clinicians and patients with ET have also been shown to prefer and adopt directional over nondirectional stimulation in a real-world setting [60]. Directional stimulation is currently available from all three device companies (Medtronic, Dublin, Ireland; Abbott Laboratories/St. Jude Medical, Chicago, IL; Boston Scientific, Marlborough, MA) that offer DBS hardware in the USA.

Sensing Technology

Sensing technology refers to detection and recording of local field potentials (LFPs) by DBS electrodes. An LFP is the summation of electrical activity from a population of neurons around an electrode. As opposed to single neuron microelectrode recordings, LFPs give information about the broader target and network electrical activity. Studies of LFP power spectra in ET have revealed that oscillatory neuronal activity in certain frequency bands is associated with tremor itself as well as tremor-producing movements like voluntary action and maintenance of posture [61]. Sensing technology was made clinically available after the 2020 FDA approval of Medtronic's Percept implantable pulse generator. This device allows for LFP recording between different electrode contacts, live streaming of a specified LFP frequency range, and remote LFP recording when patients leave the office [62]. The clinical applications are promising though yet to be fully established.

Future Directions

Adaptive/Closed-Loop DBS

Adaptive DBS (a-DBS) and closed-loop DBS (cl-DBS) are terms that are often used interchangeably due to considerable overlap in the concepts. a-DBS refers to stimulation that is not delivered constantly at fixed parameters but rather adapts in response to a given input; in the case of ET, the input might be tremor itself or a biomarker of tremor. cl-DBS refers to stimulation that adapts to such an input in an automated fashion. Theoretically, a/cl-DBS could be implemented to efficiently automate initial DBS programming as well as day-to-day stimulation parameters, ideally improving

therapeutic window, longevity of benefit, and energy expenditure. One potential input for a/cl-DBS is a kinematic wearable device with tremor detection. Kinematic-driven a/cl-DBS has been demonstrated as feasible and effective in a few case reports [63, 64]. However, the greatest current interest for the application of a/cl-DBS is utilization of LFP sensing technology as the input. One small study using LFP sensing–based a/cl-DBS demonstrated accurate tremor detection and feasibility of safe, effective, and more efficient tremor suppression [65, 66•]. There are currently at least three different registered randomized clinical trials underway investigating sensing-based a/cl-DBS (Table 2).

Other Non-continuous Stimulation Strategies

Outside of a/cl-DBS, a number of different non-continuous stimulation and program-alternating stimulation strategies have been tried in an attempt to reduce habituation and energy expenditure, ultimately with variable results [57, 67–69]. Larger studies with longer-term follow-up are needed. In addition to the numerous a/cl-DBS trials, there is at least one randomized clinical trial currently underway investigating non-continuous cyclic stimulation (Table 2).

Advanced Visualization Techniques

Advanced imaging and modeling techniques enable improvements in surgical targeting, programming, and outcomes prediction with the goal of patient specificity and eventually automaticity in DBS. Deep learning algorithms facilitate patient-specific transformation of anatomical atlases [70]. Functional MRI and diffusion tensor imaging (DTI) tractography are being used to create detailed brain connectivity maps [71, 72]. Visualization models can display LFP spectra heat maps over patient anatomic images [73]. Stimulation analytics are being used to model volume of tissue activation (VTA) based on programming parameters. VTA representation can then interact with one or all of the visualization techniques mentioned to create probabilistic models of DBS effects on anatomy, connectivity, and electrophysiology [74]. There are currently at least three registered clinical trials underway investigating functional or structural connectivity applications for DBS in ET (Table 2).

Alternative Targets

The two alternative DBS targets of greatest interest are posterior subthalamic area (PSA)/caudal zona incerta (cZI) and the dentato-rubro-thalamic tract (DRTT). A recent randomized trial comparing VIM and PSA stimulation revealed similar short-term outcomes with lower stimulation amplitudes required for PSA [75]. A post hoc analysis using DTI tractography models showed effective stimulation efficiency of either VIM or PSA was associated with proximity to the DRTT [76]. DRTT may be the true therapeutic target that runs through both VIM and PSA/cZI. No randomized studies have been performed with direct DRTT DBS, but targeting of this structure is now possible and has been performed safely and with effective DBS outcomes using tractography methods [77]. Clinical trials investigating these two targets are underway (Table 2).

Ablative Therapies

Radiofrequency

Although DBS is now considered the standard surgical treatment for ET, ablative therapies were the original surgical treatment for ET. Thalamotomies have long been performed by stereotactic neurosurgical procedures using radiofrequency (RF) ablation. RF ablations are efficacious for improvement of tremor [78], but have largely fallen out of favor with the advent of DBS due to the superior safety profile (including safety of bilateral treatment) and adjustability of DBS [40, 41, 79, 80].

Gamma Knife

In recent years, ablative therapy has made a comeback through noninvasive techniques. The idea of a noninvasive procedure, lack of implanted hardware, and no need for device programming visits are features that are appealing for many patients who may currently shy away from DBS. Noninvasive ablation was initially explored with Gamma Knife radiosurgery, which uses extracranial cobalt radiation for lesion creation. There have been reasonably safe and effective results reported in nonblinded case series [81]. However, the two blinded trials to date have shown conflicting results with the larger showing no significant tremor benefit [82, 83]. Additionally, congruent with the nature of radiation effects, lesions can take several months or more to develop. This prevents lesion refinement, limits the consistency of benefits, and can result in permanent neurologic adverse effects from unintended involvement of structures adjacent to target. Refinement and studies of this technique are ongoing though it has dropped out of favor with the emergence of ultrasound ablation techniques (Table 2).

MRI-Guided Focused Ultrasound

The most significant recent advancement in the treatment of ET is arguably the development and approval of MRI-guided focused ultrasound (MRgFUS) for thalamotomy. This technique utilizes MRI guidance for precision transcranial delivery of high-intensity focused ultrasound energy to create a

Table 2 Key ongoing clinical trials of surgical therapies in ET

Therapy class	Sponsor	Key concepts	Description	Estimated enrollment	Status	Estimated primary outcome completion date*	National Clinical Trial number
DBS	Boston Scientific	Directional	Large outcomes registry	500	Recruiting	Dec 2028	NCT04032470
	Oregon Health and Science University	Directional	Directional vs. nondirectional stimulation	24	Recruiting	Aug 2023	NCT04828798
	KU Leuven	Complex pulse shapes	Complex anodic and cathodic pulse shapes vs. standard cathodic stimulation	20	Recruiting	July 2022	NCT04725045
	University of Washington	a/cl-DBS, sensing, kinematics	a/cl-DBS driven by external sensors, thalamic sensing, cortical sensing	5	Not recruiting	Feb 2021	NCT02443181
	University of Florida	a/cl-DBS, sensing	a/cl-DBS driven by thalamic and/or cortical sensing	20	Recruiting	June 2022	NCT02649166
	University of Florida	a/cl-DBS, sensing, alternative targets	Dual lead a/cl-DBS of VIM and VO driven by same-site sensing	10	Recruiting	Dec 2024	NCT04212780
	King's College Hospital NHS Trust	Non-continuous stimulation strategies	Cyclical vs. continuous stimulation	15	Recruiting	Dec 2022	NCT04260971
	University of Minnesota	Advanced visualization techniques	DTI-based algorithmic programming	25	Recruiting	Dec 2024	NCT03984643
	University of Texas Health Science Center	Advanced visualization techniques, alternative targets	DTI and fMRI effects of DRTT DBS	72	Recruiting	Aug 2025	NCT04758624
	St. Joseph's Hospital and Medical Center	Alternative targets	VIM vs. PSA vs. VIM + PSA DBS	18	Not yet recruiting	Dec 2023	NCT05096572
MRgFUS	InSightec	—	Large outcomes registry	500	Not recruiting	Jan 2022	NCT03100474
	NYU Langone Health	Advanced visualization techniques, alternative targets	New MRI techniques for identification of DRTT	40	Recruiting	June 2022	NCT04661241
	InSightec	Staged bilateral	Safety and efficacy of staged, bilateral thalamotomy	51	Not recruiting	Mar 2022	NCT04112381
	InSightec	Staged bilateral	Safety and efficacy of ≥ 9 month staged, bilateral thalamotomy	30	Recruiting	Dec 2021	NCT03465761
	Sunnybrook Health Sciences Centre	Staged bilateral	Safety and efficacy of ≥ 48 weeks staged, bilateral thalamotomy	12	Recruiting	Oct 2022	NCT04720469
	University Health Network, Toronto	Staged bilateral	Safety and efficacy of staged, bilateral thalamotomy (BEST-FUS III)	50	Recruiting	Oct 2024	NCT04501484
Gamma Knife	Swedish Medical Center	—	Large outcomes registry	183	Not recruiting	Dec 2021	NCT02255929
	Vanderbilt University Medical Center	—	Quality of life and neuropsychiatry outcomes	60	Recruiting	Feb 2023	NCT01734122
	University Health Network, Toronto	Staged bilateral	Safety and efficacy of staged, bilateral thalamotomy	50	Recruiting	Feb 2026	NCT04748640

ET essential tremor, *DBS* deep brain stimulation, *MRgFUS* MRI-guided focused ultrasound, *a/cl-DBS* adaptive/closed-loop DBS, *VIM* ventral intermediate nucleus of the thalamus, *VO* ventral oral nucleus of the thalamus, *DTI* diffusion tensor imaging, *fMRI* functional MRI, *DRTT* dentate-rubro-thalamic tract, *PSA* posterior subthalamic area

*As per clinicaltrials.gov listing

thermal tissue ablation [84]. Tissue temperature and lesion size can be measured in real time via MRI. Lesion creation is immediate, allowing additionally for real-time monitoring of benefits and adverse effects. MRgFUS is still a relatively

new treatment with initial pilot studies in ET dating back to 2013 and FDA approval for unilateral thalamic thermoablation in medication-refractory ET attained in 2016 [85••].

Efficacy and Safety

In the pivotal randomized, double-blind sham-controlled trial that led to FDA approval, 56 ET patients underwent MRgFUS of unilateral thalamus with 47% improvement in treated hand tremor scores as well as significant improvement in quality of life and disability scores at 3-month follow-up [85••]. Benefit of 40% was sustained at 1 year in the open-label extension. The most important adverse events were paresthesias and numbness in 38% and gait disturbance in 36% of patients at 3 months. One year after the procedure, these rates declined to 14% and 9%, respectively, with 20% overall experiencing persistent neurologic adverse events. At 2-year follow-up, benefits were sustained and overall persistent neurologic adverse events declined to 17% [86]. At 3-year follow-up, there was suggestion of slight further degradation of benefit and two patients had interval resolution of neurologic adverse events [87]. At 4-year follow-up of a much smaller cohort from this trial consisting of 12 patients, benefits were sustained and no permanent neurologic adverse events persisted among these patients [88].

These results are generally supported by several non-blinded trials and subsequent meta-analyses which have shown improvement in treated hand tremor scores of around 40–80% at 3 to 6 months with similar short-term adverse event rates [89–94]. As might be anticipated with this non-invasive treatment, a comprehensive review of five of the short-term studies cited here revealed a very low rate (1.6%) of procedure-related serious adverse events [95]. Promisingly, in a very recent 2021 single-arm VIM MRgFUS trial of 35 patients, similar benefits were shown through a 1-year follow-up but with improved safety profile compared to prior studies [96]. In this trial, no serious adverse events were seen; rates of initial sensory and gait disturbances were 17.1% and 22.9%, respectively; 77.3% of adverse events resolved within the first month; adverse event rate was only 2.9% at 6 months, and all adverse events resolved by 1 year.

The longest follow-up to date is from an open-label study of 44 ET patients treated with VIM MRgFUS who were followed for 5 years [97]. Unfortunately, there was progressive dropout leaving only 5% of the original cohort by the 5-year mark, significantly limiting its usefulness. There was an initial 85% improvement in treated hand tremor scores that persisted in most of those who remained in follow-up; however during the course of follow-up, 11% of patients had return of tremor that impacted activities of daily living. The majority of neurologic adverse events resolved by 3 months but were persistent in 11% of patients.

Current Role in Relation to DBS

MRgFUS currently has a role in the treatment of ET for patients who require second-line therapies but either have a preference for a noninvasive procedure or advanced age or medical comorbidities that may elevate the risks of anesthesia and invasive neurosurgery. MRgFUS cannot be used in patients with contraindications to MRI and those with high skull thickness [98]. Efficacy appears to be similar between unilateral MRgFUS and unilateral DBS (though DBS perhaps confers greater axial tremor benefit) [99, 100•, 101]. There does appear to be some waning of effect over time, but how this compares to DBS remains to be seen and will be elucidated when longer-term follow-up is available. Although the serious procedural risks of this noninvasive procedure are lower than those of DBS, rates of sustained neurologic adverse effects demonstrated in current literature are higher with MRgFUS than with DBS [99, 100•, 101]. Given MRgFUS is an ablative therapy, the adverse events cannot be ameliorated by any adjustments after the procedure. Additionally, bilateral treatment with MRgFUS is currently neither approved nor recommended as the safety profile is expected to be worse than that of unilateral treatment [98, 102••]; this is largely extrapolated from over 60% rate of permanent gait disturbance and dysarthria with traditional thalamotomy. However, as suggested by recent unilateral and staged bilateral trials [96, 103••], it is likely that the adverse effect profile as well efficacy and longevity of benefit may continue to improve with refinement in technique and other future directions of study.

Future Directions

On the surface, MRgFUS might be viewed simply as a high-tech version of traditional ablative therapy. However, not only has this noninvasive technique essentially revived the use of ablative therapy, but the inherent properties of MRI and ultrasound technology harbor immense potential for continued advancement of precision targeting and utilization of advanced visualization techniques (previously discussed in the "Deep Brain Stimulation": "Future Directions": "Advanced Visualization Techniques" section). Two groups have performed DTI lesion analysis in MRgFUS cohorts to reveal tractographical underpinnings of greater benefit and certain adverse effects [91, 104]. Because the procedure itself is MRI-based, these findings can then be directly applied to future high-specificity target refinement. In this vein, two recent studies successfully used tractography to prospectively target VIM and DRTT (previously discussed in the "Deep Brain Stimulation": "Future Directions": "Alternative Targets" section), respectively, for ablation [105, 106].

In light of improving targeting techniques, the safety of bilateral staged MRgFUS is now being investigated as well. In a recent 2021 single-arm, single-blinded trial (BEST-FUS

Phase 2), 10 patients were treated with staged second side MRgFUS thalamotomy an average of 9 months after the first side with resultant significant benefit in quality of life measures [103••]. Adverse events with second side treatment were seen in 70% of patients (compared to 100% with first side treatment) at similar severity as first side treatment. Thirty percent had persistent mild or moderate adverse events at the 3-month follow-up, but all patients expressed that ultimately benefits outweighed the drawbacks. A phase 3 segment of this trial is currently underway along with three other registered clinical trials investigating staged bilateral procedures (Table 2).

Noninvasive Stimulation Therapies

Transcranial stimulation

The three primary techniques for transcranial stimulation are repetitive transcranial magnetic stimulation (rtMS), transcranial direct current stimulation (tDCS), and transcranial alternating current stimulation (tACS). rtMS utilizes extracranial magnetic field pulses while tDCS and tACS involve extracranial application of electrical current, each in order to modulate neuronal activation thresholds [107]. Within the current limits of these technologies, only broader and more superficial brain regions can be targeted with these modalities. Short-term, blinded, sham-controlled trials of low frequency rtMS of the cerebellum and supplementary motor area have shown slight or no improvement in tremor with minimal adverse events [108–111]. One blinded, sham-controlled trial of cerebellar tDCS showed no benefit though was well tolerated [112]. There are at least one rtMS and two tACS registered clinical trials for ET underway.

Peripheral stimulation

The primary techniques for peripheral stimulation under study for ET are functional electrical stimulation (FES) and afferent pathway stimulation [113]. FES involves stimulation of peripheral nerves or muscles above motor threshold in order to activate muscle contraction to counteract tremor. Afferent pathway stimulation involves sub-motor threshold stimulation of sensory nerve fibers in order to alter afferent signals and modulate central tremor networks. Afferent stimulation has gained more traction for practical therapeutic applications given better tolerability compared to supra-motor threshold stimulation [113]. Currently, the only FDA-approved peripheral stimulation therapy for ET is transcutaneous afferent patterned stimulation (TAPS), which involves tremor frequency-tuned delivery of alternating medial and radial nerve stimulation by a wearable wrist device called Cala Trio (Cala Health, Burlingame, CA). Evidence for the device comes from two single-session, randomized, sham-controlled trials and one large 263 patient open-label home-use trial (PROSPECT trial) which demonstrated 50% or greater improvement in tremor in more than half of patients and mild device-related adverse events (wrist discomfort, skin irritation) in 18% of patients [114, 115, 116•]. Median duration of benefit following a stimulation session was 60 min [116•, 117], which poses the primary limitation of this therapy. There are currently two registered peripheral stimulation clinical trials for ET underway.

Conclusion

ET is a very common and often disabling condition with clear necessity for improved therapeutics. Fortunately, recent therapeutic advances and future directions of development show a great deal of promise in addressing this need. A new generation of exciting pharmacologic agents specifically designed for ET is currently in clinical trials. DBS technology is advancing rapidly with two major milestones in the last few years (directional stimulation and sensing technology) and others (a/cl-DBS and advanced imaging techniques in particular) on the horizon with potential to continue improving therapeutic windows and ideally prolonging benefits. The approval of MRgFUS thalamotomy is perhaps the most significant recent advancement in the treatment of ET, offering an effective noninvasive alternative to DBS with lower procedural risks. Currently, the overall neurologic adverse effect profile is not superior to DBS; however, this new technique is quickly evolving, and the technology holds tremendous potential for advancement that may allow it to rival or even surpass DBS as the preferred interventional therapy in the future. Noninvasive stimulation techniques are under development as well with the first approved peripheral stimulation device for ET now available for clinical use.

Declarations

Conflict of Interest Neil Shetty serves as a site principal investigator for the Jazz Pharmaceuticals CX-8998 phase 2b clinical trial in essential tremor.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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