Tremor Suppression Devices

Subjects: Engineering, Biomedical

Contributor: Ronny Priefer

Tremors are the most prevalent movement disorder that interferes with the patient's daily living, and physical activities, ultimately leading to a reduced quality of life. Due to the pathophysiology of tremor, developing effective pharmacotherapies, which are only suboptimal in the management of tremor, has many challenges. Thus, a range of therapies are necessary in managing this progressive, aging-associated disorder. Surgical interventions such as deep brain stimulation are able to provide durable tremor control. However, due to high costs, patient and practitioner preference, and perceived high risks, their utilization is minimized. Medical devices are placed in a unique position to bridge this gap between lifestyle interventions, pharmacotherapies, and surgical treatments to provide safe and effective tremor suppression.

tremor medical devices transcutaneous electrical nerve stimulation electrical stimulation systems wearable orthoses assistive feeding devices

1. Introduction

Tremors, as defined by the task force of the International Parkinson and Movement Disorder Society (IPMDS), are an involuntary, rhythmic, oscillatory movement of a body part [1]. Essential tremor (ET) is recognized as the most prevalent pathological tremor among adults, affecting about 0.9% of the global population [2]. However, the true prevalence of ET may be higher, as it is believed that these patients may not seek medical attention [3]. Tremors, usually asymmetrically distributed, are frequently seen in patients with Parkinson's disease (PD), which affects more than six million individuals worldwide [4]. The presence of resting tremor supports the diagnosis of PD [5]. Different clinical subtypes and classifications of tremor disorders have also been identified [1]. The etiologies of tremor include other neurodegenerative diseases such as Wilson's disease, chromosomal aneuploidy, mitochondrial genetic disorders, infectious and inflammatory diseases, endocrine and metabolic disorders, neuropathies and spinal muscular atrophies, toxin-/drug-induced tremor pathology, and brain neoplasms and injury, as well as several environmental causes [1].

Tremors impact many aspects of the patient's daily living and interfere with many physical activities at home and in the workplace [6][7][8][9][10]. One clinical-epidemiological study compared the quality of life, including physical and psychosocial aspects, between patients with ET and PD using the Quality of Life in Essential Tremor (QUEST) questionnaire [11]. Patients with ET had a higher QUEST total score and QUEST physical subscore than patients with PD ($p < 0.05$). This suggests that patients with ET suffers significantly more physical and psychosocial impairment than those with PD [11]. Additionally, among patients suffering from tremor, their psychological strain

may be significantly more affected than their physical disabilities [6][12]. The psychological toll of tremor may extend beyond the patients themselves. The Clinical Pathological Study of Cognitive Impairment in Essential Tremor (COGNET), a longitudinal study that evaluates cognitive function in older adults with ET, reported that both patients with ET and those close to them suffer psychological stress [13]. In addition, patients may develop feelings of social isolation [11][14] and depression [6][11][13]. Due to the incredible burden put on individuals diagnosed with ET or PD, a multitude of approaches have been investigated to improve the symptoms and quality of life of those afflicted. These range from lifestyle interventions, pharmacotherapy, and surgical treatments.

Lifestyle interventions focusing on the use of weighted utensils can reduce the amplitude of tremor and alleviate the challenges patients face in their activities of daily living (ADLs) [15][16]. With additional weights, these utensils (e.g., spoon) can assist patients to eat and drink. In 2017, the National Institute for Health and Care Excellence (NICE) produced guidelines for the management of PD in adults [5]. Patients in the early stages of PD may benefit from physio- and occupational therapy if they experience motor symptoms or have difficulties with ADLs [5]. However, lifestyle and the nonpharmacological management of ET were not discussed in the guidelines produced by the American Academy of Neurology (AAN) and the IPMDS [17][18][19]. A systematic review of 19 studies found that physical therapy, limb cooling, vibration therapy, use of limb weights, bright light therapy, and transcranial magnetic stimulation were all examples of investigated treatments of tremor [20]. However, these studies mainly included convenience samples, and the long-term effectiveness of these interventions was not assessed [20].

Pharmacotherapy for the treatment of ET is suboptimal and only treats the symptoms. Many patients do not respond to the existing medications indicated for ET and do not experience a significant improvement in their daily living. Currently, propranolol and primidone are the two first-line therapies [15][16][17][18][19][21]. Across randomized controlled trials (RCTs), propranolol and primidone monotherapy produce a mean reduction in the tremor amplitude of 54.1% and 59.9%, respectively, as measured by accelerometry [22]. Nonetheless, 56.3% of patients eventually discontinued the use of either medications [23]. Topiramate is also recommended as a first-line therapy by the guidelines of the Italian Movement Disorders Association (IMDA) [24] and is considered clinically useful at higher doses by the IPMDS task force [19]. However, it is recommended by the AAN guidelines as a second-line therapy [17][18]. Second-line medications have been reported to be less efficacious in reducing the amplitude of tremors. These include alprazolam, atenolol, gabapentin, and sotalol, as well as the aforementioned topiramate [17][18]. In contrast, there is no consensus in the management of PD tremors. The current NICE guidelines recommend levodopa as the first-line therapy for management of all motor symptoms in patients in the early stages of PD [5].

Deep brain stimulation (DBS), whose efficacy has been demonstrated through closed loop approaches [25][26] and interleaving stimulation [27], is the most common surgical treatment to date, providing durable tremor control, especially for patients with medically refractory ET or advanced PD. The effectiveness of DBS in ET and PD tremor is thought to be due to the direct electrical stimulation to the ventral intermediate nucleus (VIM) possibly disrupting the synchronous firing of thalamic neurons [28][29]. In addition to the VIM, the subthalamic nucleus, internal globus pallidus, and pedunculopontine nucleus are also effective targets for DBS in patients with PD tremors [30]. The use of DBS was approved by the Food and Drug Administration (FDA) for ET in 1997, for advanced PD in 2002, and for mid-stage PD in 2016. As of late, radiofrequency thalamotomy has become less favored. An RCT comparing DBS

with thalamotomy in 68 patients with tremor due to ET, PD, or multiple sclerosis found that DBS results in fewer adverse effects (p = 0.024) and a greater increase in the Frenchay Activities Index score, which assess 15 ADLs. This suggests a greater improvement in the functional status when compared to thalamotomy [31]. Although surgical treatments for tremors, including DBS, stereotactic radiosurgery (SRS), and magnetic resonance-guided focused ultrasound (MRgFUS), are more efficacious than pharmacotherapy [32], the utilization of these procedures remains low. Limiting factors may include high surgical costs [33][34], access to care [35][36], and patient preference [35]. Other perceived barriers to DBS include practitioner preference [34][37], high resource and labor intensity [34][38], and perceptions of serious surgical risk [34][38][39].

Thus, a growing unmet need for safe and effective tremor control and suppression sets the stage for a range of therapies to bridge this gap between lifestyle modifications, pharmacotherapy, and surgical treatment. Using a variety of noninvasive suppression mechanisms, medical devices fit within this gap to provide effective tremor suppression at a lower risk than surgery. The increasing interest in this area has led to the birth of a new classification of external upper limb tremor stimulators. In 2018, the de novo classification request of Cala ONE (Cala Health, Burlingame, CA, USA) received FDA approval [40].

2. Tremor Suppression Devices: Place in Therapy

The onset of ET can occur early in childhood due to familial factors, but the majority of cases of ET appeared after the age of 40 [41]. One study investigated the correlation between the age of onset and the progression of ET in 115 patients [42]. Patients with an age of onset later than 60 years experienced a more rapid progression when compared to patients with a younger age of onset ($p < 0.001$) [42]. Since the onset of ET and PD tremors typically occurs in middle to late adulthood, aging-associated diseases such as dementia [43][44] and mild cognitive impairment [45][46][47] intersect with both of these conditions. These neurological disorders may further preclude patients from adhering to pharmacotherapies.

The medical devices described above offer alternative options for the suppression of tremors (Table 1), especially in patients who are not eligible for surgical interventions (i.e., DBS, SRS, and MRgFUS). However, the use of these devices is patient specific. For example, although Cala Trio has an aesthetic design that will likely not pose any social concerns, wearable orthoses may be a better option if the patient has any contraindication to the use of electrical stimulation systems. Depending on the patient's needs, assistive feeding devices may be a useful addition to the patient's daily living. Most of the devices that are available for use are subjected to the FDA's Class I general control for safety and efficacy assurance. In addition to the general control, Cala ONE requires Class II special control for its performance standards and special prescriber labeling.

Table 1. Summary of the tremor suppression devices and study results.

Type of Device	Study Participants (*n*)	Efficacy	Risks	Refs
Electrical Stimulation Systems: Transcutaneous Electrical Nerve Stimulators				
Cala ONE ‡	ET (77)	• Improved upper limb TETRAS tremor scores ($p = 0.017$) • Improved subject-rated BF-ADL scores ($p = 0.001$)	• Skin irritations (redness, itchiness, and swelling) • Soreness or lesions	[48]
Cala Trio *	ET (205)	• Improved upper limb TETRAS tremor scores ($p < 0.0001$) • Improved subject-rated BF-ADL scores ($p < 0.0001$)	• Discomfort (stinging and sensation of weakness) or burns	[49]
Electrical Stimulation Systems: Functional Electrical Stimulators				
MOTIMOVE	ET (3); PD tremor (4)	67% tremor suppression	Muscle fatigue	[50]
TREMOR neurorobot	ET (4); PD tremor (2)	52% tremor suppression		[51]
Tremor's glove	PD tremor (30)	Reduced UPDRS score ($p = 0.001$)		[52]
Wearable Orthoses: Active Orthoses				
WOTAS exoskeleton	ET (7); MS tremor (1); Posttraumatic tremor (1); Mixed tremor (1)	40% tremor suppression [53]	Not reported	[54] [55] [56] [53]
Pneumatic actuator-based orthosis	ET (5) §; PD tremor (5) §	98.1% tremor suppression [57]		[58] [59] [57]
PMLM-based orthosis	PD tremor (5) §	97.6% tremor suppression		[60]
Voluntary-driven	ET (1) §	99.8% tremor suppression		[61]

Type of Device	Study Participants (*n*)	Efficacy	Risks	Refs
Electrical Stimulation Systems: Transcutaneous Electrical Nerve Stimulators				
elbow orthosis				
MMS-based WTSG	Not reported	Not reported		[62]
Myoelectric-controlled orthosis	ET (2); Healthy (4)	Not reported		[63] [64] [65] [66]
Myoelectric-controlled orthosis (ver. 2)	Healthy (1)	50–80% tremor suppression [67]		[68] [67]
BSN-based orthosis	Healthy (6) §	77% tremor suppression		[69]
Wearable Orthoses: Semi-Active Orthoses				
Double viscous beam orthosis	Not reported	Not reported		[70]
MR damper-based orthosis	Not reported	Not reported		[71] [72] [73] [74]
SETS system	Not reported	Not reported	Not reported	[75]
Electromagnetic brake-based orthosis	Healthy (3) §	88% tremor suppression		[76]
Pneumatic hand cuff	ET (1)	30% tremor suppression		[77]
Wearable Orthoses: Passive Orthoses				
Tremelo *	PD tremor (1)	85% tremor suppression	Not reported	[78]
Steadi-One *	Lab simulation	85–90% tremor suppression		[79]
Readi-Steadi *	ET (20); Healthy (40)	50% tremor suppression		[80]
Task-Adjustable Passive Orthosis	PD tremor (1)	• 82% tremor suppression while drinking (p = 0.03)		[81]

Type of Device	Study Participants (*n*)	Efficacy	Risks	Refs
Electrical Stimulation Systems: Transcutaneous Electrical Nerve Stimulators				
		• 79% tremor suppression while pouring ($p = 0.03$) • 74% tremor suppression while drawing a spiral ($p = 0.03$)		
Particle Damper	Not reported	Not reported		[82]
Vib-Bracelet	PD tremor (1) §	85% tremor suppression		[83] [84]
Air-dashpot-based orthosis	Healthy (1) ¶	• 20–62% tremor suppression in the wrist • 82% tremor suppression in the elbow		[85]
Assistive Feeding Devices				
Neater Eater *	Not reported	Not reported		[86]
Liftware Steady *	ET (15)	• Improved FTM-TRS while holding, eating, and transferring objects ($p = 0.001$) • 73% tremor suppression	Not reported	[87]
Gyenno Spoon *	Not reported	85% tremor suppression (claimed)		[88]
Gyroscopic Stabilizers				
GyroGlove *	Not reported	Not reported	Not reported	[89]

5. National Institute for Health and Care Excellence (UK). Parkinson's Disease in Adults: Diagnosis and Management; National Institute for Health and Care Excellence (UK): London, UK, 2017.

Type of Device	Study Participants (*n*)	Efficacy	Risks	Refs
Electrical Stimulation Systems: Transcutaneous Electrical Nerve Stimulators				
Haptic Stimulation Systems				
Emme Watch	Not reported	Not reported	Not reported	

BF-ADL, Bain and Findley Activities of Daily Living; BSN, body sensor network; ET, essential tremor; FTM-TRS, Fahn-Tolosa-Marin Tremor Rating Scale; MMS, multi-channel mechatronic splitter; MS, multiple sclerosis; PMLM, permanent magnet linear motor; SETS, soft exoskeleton for tremor suppression; TETRAS, Tremor Research Group Essential Tremor Rating Assessment Scale; PD, Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale; WoTAS, Wearable Orthosis for Tremor Assessment and Suppression; and WTSG, wearable tremor suppression gloves. † FDA-registered, Class I medical device. ‡ FDA-approved; Class II medical device. § Test bench simulation. ¶ Induced muscle-contraction.

ET is associated with a staggering cost of direct medical expenses, indirect productivity and income losses, nonmedical expenses, and disability benefits. The unemployment rate increases to about 88% in patients whose ET progresses from mild to severe [90], leading to forced early retirements. Collectively, patients with mild ET have a 1.83-year average loss of employment, corresponding to a $280 billion in income loss [90]. In patients with moderate to severe tremors, the average loss of employment is 6.5 years [90]. ET and PD tremors likely increase the economic burden more than currently estimated due to their progressive natures and the underreported cases.

The development of a medical device for tremor suppression is an under-researched area. Most of the investigational devices discussed were abandoned before entering the market. However, it is imperative that the search for safe and effective tremor suppression devices continues, given the overall economic burden of tremors. Given that most of the currently available devices are based on preliminary data, more investigation is needed to understand the safety and efficacy of these devices before their use in clinical practice can be supported. Cost-effectiveness data are necessary and important to convince insurance programs to provide coverage, alleviating the economic burden on patients and caregivers.

3. Future Perspectives

The devices currently studied have employed distinctive mechanistic approaches. The weight of evidence supporting their efficacy challenges the notion that tremors originate from a single, dominant pathway. Additional pathological insights, such as the loss of Purkinje cells in ET [91][92] and increased central oscillator synchronization in the basal ganglia in PD tremors [93], along with several mechanistic targets of tremor suppression devices, highlight the advances in our understanding of how tremors may be generated. Perhaps the most pertinent

8. Héroux, M.E.; Parisi, S.L.; Larocerie-Salgado, J.; Norman, K.E. Upper-Extremity Disability in Essential Tremor. Arch. Phys. Med. Rehabil. 2006, 87, 661–670.
9. Norman, K.E.; D'Amboise, S.N.; Pari, G.; Héroux, M.E. Tremor during movement correlates well with disability in people with essential tremor. Mov. Disord. 2011, 26, 2088–2094.
10. Rajput, A.H.; Robinson, C.A. Essential tremor course and disability: A clinicopathologic study of 20 cases. Neurology 2004, 62, 932–936.
11. Louis, E.D.; Machado, D.G. Tremor-related quality of life: A comparison of essential tremor vs. Parkinson's disease patients. Park. Relat. Disord. 2015, 21, 729–735.
12. Lorenz, D.; Schwieger, D.; Moises, H.; Deuschl, G. Quality of life and personality in essential tremor patients. Mov. Disord. 2006, 21, 1114–1118.
13. Monin, J.K.; Gutierrez, J.; Kellner, S.; Morgan, S.; Collins, K.; Rohl, B.; Migliore, F.; Cosentino, S.; Huey, E.; Louis, E.D. Psychological Suffering in Essential Tremor: A Study of Patients and Those Who Are Close to Them. Tremor Other Hyperkinetic Mov. 2017, 7, 526.
14. Schneier, F.R.; Barnes, L.F.; Albert, S.M.; Louis, E.D. Characteristics of Social Phobia among Persons with Essential Tremor. J. Clin. Psychiatry 2001, 62, 367–372.
15. Damen, J.A.A.G. Author's reply to Woodward. BMJ 2016, 354, i4485.
16. Elias, W.J.; Shah, B.B. Tremor. JAMA 2014, 311, 948–954.
17. Zesiewicz, T.A.; Elble, R.; Louis, E.D.; Hauser, R.A.; Sullivan, K.L.; Dewey, R.B.; Ondo, W.G.; Gronseth, G.S.; Weiner, W.J. Practice Parameter: Therapies for essential tremor: Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2005, 64, 2008–2020.
18. Zesiewicz, T.A.; Elble, R.J.; Louis, E.D.; Gronseth, G.S.; Ondo, W.G.; Dewey, R.B.; Okun, M.S.; Sullivan, K.L.; Weiner, W.J. Evidence-based guideline update: Treatment of essential tremor: Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2011, 77, 1752–1755.
19. Ferreira, J.J.; Mestre, T.A.; Lyons, K.E.; Benito-León, J.; Tan, E.; Abbruzzese, G.; Hallett, M.; Haubenberger, D.; Elble, R.; Deuschl, G.; et al. MDS evidence-based review of treatments for essential tremor. Mov. Disord. 2019, 34, 950–958.

20. O'Connor, R.J.; Kini, M.U. Non-pharmacological and non-surgical interventions for tremor: A systematic review. Park. Relat. Disord. 2011, 17, 509–515.
21. Haubenberger, D.; Hallett, M. Essential Tremor. N. Engl. J. Med. 2018, 378, 1802–1810.
22. Deuschl, G.; Raethjen, J.; Hellriegel, H.; Elble, R. Treatment of patients with essential tremor. Lancet Neurol. 2011, 10, 148–161.
23. Diaz, N.L.; Louis, E.D. Survey of medication usage patterns among essential tremor patients: Movement disorder specialists vs. general neurologists. Park. Relat. Disord. 2010, 16, 604–607.
24. Zappia, M.; Italian Movement Disorders Association (DISMOV-SIN) Essential Tremor Committee; Albanese, A.; Bruno, E.; Colosimo, C.; Filippini, G.; Martinelli, P.; Nicoletti, A.; Quattrocchi, G. Treatment of essential tremor: A systematic review of evidence and recommendations from the Italian Movement Disorders Association. J. Neurol. 2012, 260, 714–740.
25. Velisar, A.; Syrkin-Nikolau, J.; Blumenfeld, Z.; Trager, M.; Afzal, M.; Prabhakar, V.; Bronte-Stewart, H. Dual threshold neural closed loop deep brain stimulation in Parkinson disease patients. Brain Stimul. 2019, 12, 868–876.
26. Weerasinghe, G.; Duchet, B.; Cagnan, H.; Brown, P.; Bick, C.; Bogacz, R. Predicting the effects of deep brain stimulation using a reduced coupled oscillator model. PLoS Comput. Biol. 2019, 15, e1006575.
27. Kern, D.S.; Picillo, M.; Thompson, J.A.; Sammartino, F.; Di Biase, L.; Munhoz, R.P.; Fasano, A. Interleaving Stimulation in Parkinson's Disease, Tremor, and Dystonia. Ster. Funct. Neurosurg. 2018, 96, 379–391.
28. Chen, K.S.; Chen, R. Invasive and Noninvasive Brain Stimulation in Parkinson's Disease: Clinical Effects and Future Perspectives. Clin. Pharmacol. Ther. 2019, 106, 763–775.
29. Farokhniaee, A.; McIntyre, C.C. Theoretical principles of deep brain stimulation induced synaptic suppression. Brain Stimul. 2019, 12, 1402–1409.
30. Mao, Z.; Ling, Z.; Pan, L.; Xu, X.; Cui, Z.; Liang, S.; Yu, X. Comparison of Efficacy of Deep Brain Stimulation of Different Targets in Parkinson's Disease: A Network Meta-Analysis. Front. Aging Neurosci. 2019, 11, 23.
31. Schuurman, P.R.; Bosch, D.A.; Bossuyt, P.M.; Bonsel, G.J.; Van Someren, E.J.; De Bie, R.M.; Merkus, M.P.; Speelman, J.D. A Comparison of Continuous Thalamic Stimulation and Thalamotomy for Suppression of Severe Tremor. N. Engl. J. Med. 2000, 342, 461–468.
32. Elble, R.J.; Shih, L.; Cozzens, J.W. Surgical treatments for essential tremor. Expert Rev. Neurother. 2018, 18, 303–321.
33. Ravikumar, V.K.; Parker, J.J.; Hornbeck, T.S.; Santini, V.E.; Pauly, K.B.; Wintermark, M.; Ghanouni, P.; Stein, S.C.; Halpern, C.H. Cost-effectiveness of focused ultrasound, radiosurgery,

and DBS for essential tremor. Mov. Disord. 2017, 32, 1165–1173.

34. Lozano, A.M.; Lipsman, N.; Bergman, H.; Brown, P.; Chabardes, S.; Chang, J.W.; Matthews, K.; McIntyre, C.C.; Schlaepfer, T.E.; Schulder, M.; et al. Deep brain stimulation: Current challenges and future directions. Nat. Rev. Neurol. 2019, 15, 148–160.
35. Walters, H.; Shah, B.B. Focused Ultrasound and Other Lesioning Therapies in Movement Disorders. Curr. Neurol. Neurosci. Rep. 2019, 19, 66.
36. Chan, A.K.; McGovern, R.A.; Brown, L.T.; Sheehy, J.P.; Zacharia, B.E.; Mikell, C.B.; Bruce, S.S.; Ford, B.; McKhann, G.M. Disparities in Access to Deep Brain Stimulation Surgery for Parkinson Disease. JAMA Neurol. 2014, 71, 291–299.
37. Lange, M.; Mauerer, J.; Schlaier, J.; Janzen, A.; Zeman, F.; Bogdahn, U.; Brawanski, A.; Hochreiter, A. Underutilization of deep brain stimulation for Parkinson's disease? A survey on possible clinical reasons. Acta Neurochir. 2017, 159, 771–778.
38. Shukla, A.W.; Deeb, W.; Patel, B.; Ramirez-Zamora, A. Is deep brain stimulation therapy underutilized for movement disorders? Expert Rev. Neurother. 2018, 18, 899–901.
39. Kim, M.-R.; Yun, J.Y.; Jeon, B.; Lim, Y.H.; Kim, K.R.; Yang, H.-J.; Paek, S.H. Patients' reluctance to undergo deep brain stimulation for Parkinson's disease. Park. Relat. Disord. 2016, 23, 91–94.
40. Food and Drug Administration. Medical Devices; Neurological Devices; Classification of the External Upper Limb Tremor Stimulator. Final order. Fed. Regist. 2018, 83, 52315–52316.
41. Louis, E.D. The Roles of Age and Aging in Essential Tremor: An Epidemiological Perspective. Neuroepidemiology 2019, 52, 111–118.
42. Louis, E.D.; Ford, B.; Barnes, L.F. Clinical subtypes of essential tremor. Arch. Neurol. 2000, 57, 1194–1198.
43. Benito-León, J.; Louis, E.D.; Bermejo-Pareja, F. Elderly-onset essential tremor is associated with dementia. Neurology 2006, 66, 1500–1505.
44. Hanagasi, H.A.; Tufekcioglu, Z.; Emre, M. Dementia in Parkinson's disease. J. Neurol. Sci. 2017, 374, 26–31.
45. Park, I.-S.; Oh, Y.-S.; Lee, K.-S.; Yang, D.-W.; Song, I.-U.; Park, J.-W.; Kim, J.-S. Subtype of Mild Cognitive Impairment in Elderly Patients with Essential Tremor. Alzheimer Dis. Assoc. Disord. 2015, 29, 141–145.
46. Benito-León, J.; Louis, E.D.; Mitchell, A.J.; Bermejo-Pareja, F. Elderly-Onset Essential Tremor and Mild Cognitive Impairment: A Population-Based Study (NEDICES). J. Alzheimer's Dis. 2011, 23, 727–735.

47. Monastero, R.; Cicero, C.E.; Baschi, R.; Davì, M.; Luca, A.; Restivo, V.; Zangara, C.; Fierro, B.; Zappia, M.; Nicoletti, A. Mild cognitive impairment in Parkinson's disease: The Parkinson's disease cognitive study (PACOS). J. Neurol. 2018, 265, 1050–1058.
48. Pahwa, R.; Dhall, R.; Ostrem, J.; Gwinn, R.; Lyons, K.; Ro, S.; Dietiker, C.; Luthra, N.; Ms, P.C.; Hamner, S.; et al. An Acute Randomized Controlled Trial of Noninvasive Peripheral Nerve Stimulation in Essential Tremor. Neuromodulation 2018, 22, 537–545.
49. Isaacson, S.H.; Peckham, E.; Tse, W.; Waln, O.; Way, C.; Petrossian, M.T.; Dahodwala, N.; Soileau, M.J.; Lew, M.; Dietiker, C.; et al. Prospective Home-use Study on Non-invasive Neuromodulation Therapy for Essential Tremor. Tremor Other Hyperkinetic Mov. 2020, 10, 29.
50. Maneski, L.P.; Jorgovanović, N.; Ilić, V.; Došen, S.; Keller, T.; Popović, M.B.; Popović, D.B. Electrical stimulation for the suppression of pathological tremor. Med. Biol. Eng. Comput. 2011, 49, 1187–1193.
51. Gallego, J.Á.; Rocon, E.; Belda-Lois, J.M.; Pons, J.L. A neuroprosthesis for tremor management through the control of muscle co-contraction. J. Neuroeng. Rehabil. 2013, 10, 36.
52. Jitkritsadakul, O.; Thanawattano, C.; Anan, C.; Bhidayasiri, R. Tremor's glove-an innovative electrical muscle stimulation therapy for intractable tremor in Parkinson's disease: A randomized sham-controlled trial. J. Neurol. Sci. 2017, 381, 331–340.
53. Rocón, E.; Belda-Lois, J.M.; Ruiz, A.; Manto, M.; Moreno, J.C.; Pons, J.L. Design and Validation of a Rehabilitation Robotic Exoskeleton for Tremor Assessment and Suppression. IEEE Trans. Neural Syst. Rehabil. Eng. 2007, 15, 367–378.
54. Rocon, E.; Ruiz, A.; Pons, J.L.; Belda-Lois, J.; Sánchez-Lacuesta, J. Rehabilitation Robotics: A Wearable Exo-Skeleton for Tremor Assessment and Suppression. In Proceedings of the Proceedings of the 2005 IEEE International Conference on Robotics and Automation, Barcelona, Spain, 18–22 April 2005.
55. Rocon, E.; Ruiz, A.; Brunetti, F.; Pons, J.L.; Belda-Lois, J.; Sánchez-Lacuesta, J. On the use of an active wearable exoskeleton for tremor suppression via biomechanical loading. In Proceedings of the 2006 IEEE International Conference on Robotics and Automation, Orlando, FL, USA, 15–19 May 2006.
56. Manto, M.; Rocon, E.; Pons, J.L.; Belda, J.M.; Camut, S. Evaluation of a wearable orthosis and an associated algorithm for tremor suppression. Physiol. Meas. 2007, 28, 415–425.
57. Taheri, B.; Case, D.; Richer, E. Adaptive Suppression of Severe Pathological Tremor by Torque Estimation Method. IEEE/ASME Trans. Mechatron. 2014, 20, 717–727.
58. Taheri, B.; Case, D.; Richer, E. Active Tremor Estimation and Suppression in Human Elbow Joint. In Proceedings of the ASME 2011 Dynamic Systems and Control Conference, Arlington, VI, USA, 31 October–2 November 2011.

59. Taheri, B.; Case, D.; Richer, E. Robust Controller for Tremor Suppression at Musculoskeletal Level in Human Wrist. IEEE Trans. Neural Syst. Rehabil. Eng. 2013, 22, 379–388.
60. Zamanian, A.H.; Richer, E. Adaptive disturbance rejection controller for pathological tremor suppression with permanent magnet linear motor. In Proceedings of the ASME 2017 Dynamic Systems and Control Conference, Tysons, VI, USA, 11–13 October 2017.
61. Herrnstadt, G.; Menon, C. Voluntary-Driven Elbow Orthosis with Speed-Controlled Tremor Suppression. Front. Bioeng. Biotechnol. 2016, 4, 29.
62. Zhou, Y.; Naish, M.D.; Jenkins, M.E.; Trejos, A.L. Design and validation of a novel mechatronic transmission system for a wearable tremor suppression device. Robot. Auton. Syst. 2017, 91, 38–48.
63. Ando, T.; Watanabe, M.; Fujie, M.G. Extraction of voluntary movement for an EMG controlled exoskeltal robot of tremor patients. In Proceedings of the 2009 4th International IEEE/EMBS Conference on Neural Engineering, Antalya, Turkey, 29 April–2 May 2009.
64. Seki, M.; Matsumoto, Y.; Ando, T.; Kobayashi, Y.; Fujie, M.G.; Iijima, H.; Nagaoka, M. Development of robotic upper limb orthosis with tremor suppressiblity and elbow joint movability. In Proceedings of the 2011 IEEE International Conference on Systems, Man, and Cybernetics, Anchorage, AK, USA, 9–12 October 2011.
65. Seki, M.; Matsumoto, Y.; Ando, T.; Kobayashi, Y.; Iijima, H.; Nagaoka, M.; Fujie, M.G. The weight load inconsistency effect on voluntary movement recognition of essential tremor patient. In Proceedings of the 2011 IEEE International Conference on Robotics and Biomimetics, Karon Beach, Thailand, 7–11 December 2011.
66. Ando, T.; Watanabe, M.; Nishimoto, K.; Matsumoto, Y.; Seki, M.; Fujie, M.G. Myoelectric-Controlled Exoskeletal Elbow Robot to Suppress Essential Tremor: Extraction of Elbow Flexion Movement Using STFTs and TDNN. J. Robot. Mechatron. 2012, 24, 141–149.
67. Matsumoto, Y.; Seki, M.; Ando, T.; Kobayashi, Y.; Nakashima, Y.; Iijima, H.; Nagaoka, M.; Fujie, M.G. Development of an Exoskeleton to Support Eating Movements in Patients with Essential Tremor. J. Robot. Mechatron. 2013, 25, 949–958.
68. Matsumoto, Y.; Amemiya, M.; Kaneishi, D.; Nakashima, Y.; Seki, M.; Ando, T.; Kobayashi, Y.; Iijima, H.; Nagaoka, M.; Fujie, M.G. Development of an elbow-forearm interlock joint mechanism toward an exoskeleton for patients with essential tremor. In Proceedings of the 2014 IEEE/RSJ International Conference on Intelligent Robots and Systems, Chicago, IL, USA, 14–18 September 2014.
69. Huen, D.; Liu, J.; Lo, B. An integrated wearable robot for tremor suppression with context aware sensing. In Proceedings of the 2016 IEEE 13th International Conference on Wearable and Implantable Body Sensor Networks (BSN), San Francisco, CA, USA, 14–17 June 2016.

70. Loureiro, R.; Belda-Lois, J.M.; Lima, E.; Pons, J.; Sanchez-Lacuesta, J.; Harwin, W.S. Upper Limb Tremor Suppression in ADL Via an Orthosis Incorporating a Controllable Double Viscous Beam Actuator. In Proceedings of the 9th International Conference on Rehabilitation Robotics, Chicago, IL, USA, 28 June–1 July 2005.
71. Case, D.; Taheri, B.; Richer, E. Dynamic Magnetorheological Damper for Othotic Tremor Suppression. In Proceedings of the 2011 Hawaii University International Conference on Mathematics and Engineering, Honolulu, HI, USA, 13–15 June 2011.
72. Case, D.; Taheri, B.; Richer, E. Multiphysics modeling of magnetorheological dampers. Int. J. Multiphysics 2013, 7, 61–76.
73. Case, D.; Taheri, B.; Richer, E. A Lumped-Parameter Model for Adaptive Dynamic MR Damper Control. IEEE ASME Trans. Mechatron. 2014, 20, 1–8.
74. Case, D.; Taheri, B.; Richer, E. Active control of MR wearable robotic orthosis for pathological tremor suppression. In Proceedings of the ASME 2015 Dynamic Systems and Control Conference, Columbus, OH, USA, 28–30 October 2015.
75. Zahedi, A.; Zhang, B.; Yi, A.; Zhang, D. A Soft Exoskeleton for Tremor Suppression Equipped with Flexible Semiactive Actuator. Soft Robot. 2020.
76. Herrnstadt, G.; Menon, C. On-Off Tremor Suppression Orthosis with Electromagnetic Brake. Int. J. Mech. Eng. Mechatron. 2013, 1, 7–14.
77. Kalaiarasi, A.; Kumar, L.A. Sensor Based Portable Tremor Suppression Device for Stroke Patients. Electrother. Res. 2018, 43, 29–37.
78. Rudraraju, S.; Nguyen, T. Wearable Tremor Reduction Device (TRD) for Human Hands and Arms. In Proceedings of the 2018 Design of Medical Devices Conference, Minneapolis, MI, USA, 9–12 April 2018.
79. Elias, M.; Patel, S.; Maamary, E.; Araneta, L.; Obaid, N. Apparatus for Damping Involuntary Hand Motions. U.S. Patent 0,216,628 A1, 18 July 2019.
80. Hunter, R.; Pivach, L.; Madere, K.; Van Gemmert, A.W.A. Potential benefits of the Readi-Steadi on essential tremor. In Proceedings of the 5th Annual LSU Discover Day, Baton Rouge, LA, USA, 10 April 2018.
81. Fromme, N.P.; Camenzind, M.; Riener, R.; Rossi, R.M. Design of a lightweight passive orthosis for tremor suppression. J. Neuroeng. Rehabil. 2020, 17, 1–15.
82. Lu, Z.; Huang, Z. Analytical and experimental studies on particle damper used for tremor suppression. J. Vib. Control 2020, 1–11.
83. Katz, R.; Buki, E.; Zacksenhouse, M. Attenuating Tremor Using Passive Devices. Stud. Health Technol. Inform. 2017, 242, 741–747.

84. Buki, E.; Katz, R.; Zacksenhouse, M.; Schlesinger, I. Vib-bracelet: A passive absorber for attenuating forearm tremor. Med Biol. Eng. Comput. 2017, 56, 923–930.
85. Takanokura, M.; Sugahara, R.; Miyake, N.; Ishiguro, K.; Muto, T.; Sakamoto, K. Upper-limb orthoses implemented with air dashpots for suppression of pathological tremor in daily activities. In Proceedings of the 23rd Congress of International Society of Biomechanics, Brussels, Belgium, 2–3 July 2011.
86. Michaelis, J. Introducing the neater eater. Action Res. 1988, 6, 2–3.
87. Pathak, A.; Redmond, J.A.; Allen, M.; Chou, K.L. A noninvasive handheld assistive device to accommodate essential tremor: A pilot study. Mov. Disord. 2013, 29, 838–842.
88. Zhu, Y.; Ren, K. Arm Vibration Damping Device. U.S. Patent 0,327,023 A1, 16 November 2017.
89. De Panisse, P.; Ibrahim, Y.; Medeisis, J.; Tiarvando, L.; Vaklev, N.L.; Ong, J.F.; Gan, B.; Koh, B.; Soler, X.L.; Choong Ngan Lou, W. Tremor Stabilization Apparatus and Methods. U.S. Patent 0266820 A1, 20 September 2018.
90. Frost & Sullivan. Assessing the Full Impact of Essential Tremor on Patient Quality of Life and Finances in the United States. 2018. Available online: (accessed on 20 September 2020).
91. Axelrad, J.E.; Louis, E.D.; Honig, L.S.; Flores, I.; Ross, G.W.; Pahwa, R.; Lyons, K.E.; Faust, P.L.; Vonsattel, J.P.G. Reduced Purkinje Cell Number in Essential Tremor. Arch. Neurol. 2008, 65, 101–107.
92. Louis, E.D.; Lee, M.; Babij, R.; Ma, K.; Cortés, E.; Vonsattel, J.-P.G.; Faust, P.L. Reduced Purkinje cell dendritic arborization and loss of dendritic spines in essential tremor. Brain 2014, 137, 3142–3148.
93. Helmich, R.C.; Janssen, M.J.R.; Oyen, W.J.G.; Bloem, B.R.; Toni, I. Pallidal dysfunction drives a cerebellothalamic circuit into Parkinson tremor. Ann. Neurol. 2011, 69, 269–281.
94. Espay, A.J.; Lang, A.E.; Erro, R.; Merola, A.; Fasano, A.; Berardelli, A.; Bhatia, K.P. Essential pitfalls in “essential” tremor. Mov. Disord. 2017, 32, 325–331.