Advanced Journal of Graduate Research
ISSN:2456-7108
Volume 13, Issue 1, pp. 29-36, January 2023
DOI: https://doi.org/10.21467/ajgr.13.1.29-36

GRADUATE REVIEWS

Why is Essential Tremor so Difficult to Treat? A Literature Review

Anna KA Dinh[1], A Janet Adeoti[2], Nicholas DJ Strzalkowski[1,3*]

[1] Faculty of Science and Technology, Mount Royal University, Alberta, Canada
[2] Department of Clinical Neuroscience, University of Calgary, Alberta, Canada
[3] Faculty of Teaching and Learning, Mount Royal University, Alberta, Canada

* Corresponding Author email: nstrzalkowski@mtroyal.ca

Article History

Received: 24 August 2022
Revised: 13 February 2023
Accepted: 14 February 2023
Published: 24 February 2023

Student(s)

- Anna Kieu Anh Dinh

Academic Year: 2021-2022
Course Level: Bachelor
Course Name: B.Sc.
Course year: 4th year

- Adesewa Janet Adeoti

Academic Year: 2021-2022
Course Level: Master
Course Name: M.Sc.
Course year: 2nd year

Mentor(s)

- Dr. Nicholas Donald James Strzalkowski

ABSTRACT

Essential tremor (ET) is the most common movement disorder and affects tens of millions of individuals worldwide. It is characterized by isolated upper-limb tremors for at least three years without other neurological signs or tremors in other locations. Despite ET being a widespread movement disorder, its etiology and pathophysiology are poorly understood. This lack of understanding poses significant challenges towards the development of treatments and cures. There is no cure for ET, and current treatments for ET are limited and are often insufficient. ET symptoms can differ greatly between patients, and phenotyping is the only method for diagnosis. ET often overlaps with other disorders including dystonia and Parkinson's disease, which further complicates diagnosis and treatment. Current treatments begin with pharmacotherapy, and progress to surgical options in drug-resistant patients. There is ongoing research into non-invasive electrical stimulation treatments that may prove to be safe and effective; however, further research is needed. The aim of this review is to assess the literature and summarize why ET is so difficult to treat. We evaluate the efficacy of current treatments, and the potential of future treatments. We summarize four reasons why ET remains so difficult to treat: 1) the unknown etiology and pathophysiology, 2) the lack of a suitable animal model, 3) difficulties with diagnosis, and 4) absence of personalized treatments. Despite the current challenges, ET remains an active area of research and novel experimental treatments may produce safe and effective non-invasive therapeutic options for ET.

Keywords: Essential tremor, pathophysiology, treatment

1 Introduction

Essential tremor (ET) is the most common movement disorder and affects over 60 million individuals worldwide [1]. Despite its high prevalence, disease mechanisms are poorly understood, and treatment options remain limited and ineffective for most patients. Here we reviewed the literature to address the question *why does ET remain so difficult to treat?* We arrived at four primary conclusions: 1) unknown etiology and pathophysiology, 2) lack of animal models, 3) difficulties with diagnosis, and 4) lack of personalized treatments. We acknowledge that there are other important issues to address and provide this list as one perspective. ET remains a widespread and complex movement disorder with many outstanding research questions that need to be addressed to improve treatment options for patients.

ET is characterized by isolated bilateral upper-limb action tremor for at least three years, without neurological signs of tremors in other locations such as the larynx, head, and lower limbs [1], [2]. ET manifests as involuntary, oscillating, or twitching movements that occur while moving or at rest [1] Different tremor types (rest, postural, and kinetic) can be present in ET patients; however, ET is primarily considered an action tremor that occurs with voluntary activation of affected muscles. Action tremor can be further divided into postural tremor (while maintaining a position against gravity) or kinetic tremor (during voluntary movement like eating) [2]. ET is a multifactorial disorder, i.e., multiple factors may contribute to its development. The heterogeneous nature of ET has led to disparities and ongoing debates about its diagnosis, etiology, and pathophysiology. It is important for the clinical and research community to reach a consensus as many individuals with ET face a significantly reduced quality of life. Tremors can hinder activities requiring fine motor skills such as writing, eating, drinking, or tying a shoelace. The economic burden of ET in the United States is over 140 billion USD annually and about 88% of individuals with ET are unemployed due to their disability [1].

ET is equally prevalent in men and women and can occur at any age [3]. The global prevalence for ET is estimated to be 3.2 out of 1000 individuals, which increases with advanced age to 28.7 cases per 1000 individuals over the age of 80 [1]. The general risk factors for ET are primarily positive family history and aging. Positive family history is associated with early-onset familial ET, while aging is more related with sporadic ET [4]. There are two peaks of onset: young-onset (<25 years old) and late-onset (>65 years old) [5]. The young onset of ET is often associated with heritability, although there have been cases that ET has no linkage to family history [1], [6]. Young onset is considered familial ET, consistent with autosomal dominant transmission [1]. Approximately 20% to 90% of ET patients have a positive family history, which suggests that genetics may be a factor in the development of ET [6]. However, there is a lack of conclusive evidence on what genes are involved in the disorder and current genetic studies have many limitations including clinical heterogeneity, genetic heterogeneity, incomplete clinical penetrance, small sample sizes, and ET-like phenotype in other genetic syndromes. The prevalence of late-onset ET is about 4.6-6.3% of the population and are typically categorized as sporadic ET [1], [6]. Late-onset patients typically do not have an identifiable cause with absent family history [1], [6]. The occurrence of sporadic cases of ET with no family history suggests that there are other factors at play besides genetics [1]. This illustrates the complexity of ET's etiology and the challenges facing diagnosis and treatment.

Current treatments for ET include pharmacotherapy, of which the three most used pharmaceuticals are propranolol, primidone, and topiramate [1], [6]. For drug resistant patients, surgical and non-invasive electrical stimulation treatments are available. Surgical treatments are invasive and include deep brain stimulation and thalamotomy [1], [6], [7]. There are various types of thalamotomy procedures available such as MRI-guided focused ultrasound and gamma knife radiosurgery [1], [6], [7]. Non-invasive electrical stimulation treatments include transcranial alternating current stimulation (tACS), transcranial magnetic stimulation (TMS), and peripheral electrical stimulation [1], [6]–[8]. However, there have been limited studies and no randomized controlled trials to compare the efficacy and risks of these non-invasive treatments [1], [6], [7]. This means that the timeline and efficacy for non-invasive treatments for ET remain uncertain despite ongoing research. Further investigations and clinical studies are required to better understand the underlying relationship between the neurological, pathophysiology, and genetics of ET to advance therapeutic options.

Despite the great efforts made by clinicians and researchers to understand the etiology and pathophysiology of ET, the underlying disease mechanisms remain unknown which complicates the progress of developing a reliable treatment and/or cure. Furthermore, a suitable animal model does not exist for ET, which hinders the means of finding experimental information about diagnosis, pathophysiology, and treatments. Multiple studies using a diverse range of animals only show a single feature or some of the symptoms that humans show with ET [1]. In addition, to diagnose ET clinicians are limited to phenotyping, which typically takes 3-years. Lastly, current experimental treatments that are being used lack personalization, where each patient

requires treatments that are specific to their needs. However, with more research, novel experimental treatments may emerge to be safe and effective at treating ET.

2 Unknown Etiology and Pathophysiology

The etiology and pathophysiology of ET are poorly understood, which has contributed to a lack of reliable treatment options or the development of a cure. There have been several studies focused on the genetic components of ET with the goal to identify genetic factors; however, the genetics of ET remain complex [1], [9]–[11]. The most notable genes associated with a risk of developing ET have been identified as *LINGO1*, *NOTCH2, NLC, EAAT2, SORT1*, SLC1A2, SCN4A, NOS3, and KCN52 [6]. The associations of these genes with ET indicates that genetics can play a role in the development of ET [6], [10], [11] Despite this genetic link, many patients develop sporadic ET, and it remains unclear the extent to which these genes confer the risk of developing ET.

Proposed mechanisms of ET also include the presence of brainstem Lewy bodies, gradual loss of Purkinje fibers, and presence of torpedoes that aid in the pathophysiology of ET [12]. However, research on these proposed mechanisms report contrasting results [6], [12]. There remains no consensus on the role of different neurological changes observed in ET [1], [6]. This gap in knowledge is important as it shows that there is a lack of understanding of the etiology and pathophysiology of ET, which in turn makes it difficult to develop a reliable treatment for ET.

Despite the uncertainty about exact mechanisms, recent studies have increased support for cerebellar-thalamic-cortical-circuitry dysfunction as a key player in ET [1]. It is thought that abnormal oscillations within the cerebellar-thalamic-cortical circuitry may be responsible for the generation of tremor. Additionally, gamma aminobutyric acid (GABA) dysfunction within the nervous system has been a long-term proposed mechanism of ET. GABA is an inhibitory neurotransmitter and ET patients have been reported to have low GABA levels in the cerebellum [1], [9]. However, a study found that a lack of Purkinje fibres with GABA neurotransmissions does not result in pathological tremors [11], [13]. Furthermore, pharmaceuticals such as primidone and topiramate have been shown to improve GABAergic transmission and reduce ET symptoms, which indicates that GABA may play a potential role in the development of ET [14]. Nevertheless, recent neuroimaging studies have viewed GABA levels in the dentate nucleus of ET patients and found that there are no changes [14]. It is important to keep note that the abnormalities observed in GABAergic transmission in ET patients lack a genetic component to them as currently no correlation has been found between the heterogeneity transporters and receptors for GABA and ET [13], [14].

In addition to genetic and neural circuitry components, environmental factors are also thought to play a role in the development and progression of ET. Dietary factors such as alcohol and caffeine intake, and B carboline alkaloids have been shown to be associated with the development of ET [1], [6], [14]. However, the research is far from reaching a consensus on these associations [1]. Due to variable penetrance and difficulties in validating data in both genetics and dietary factors, conclusions about the relative role of genetic-environment contributions to ET are difficult to make. Moreover, a cure for ET is particularly difficult to establish as there is no exact causal gene or specific physiological dysfunction in ET. As the contributions of both genetic and environmental factors are poorly understood, as well as the pathophysiology and etiology of ET, the outlook for a reliable treatment remains an area of ongoing work.

3 Lack of a Suitable Animal Model

Animal models are an important experimental means to obtain information about disorders and/or diseases, preventions, diagnosis, and treatments. Having a suitable animal model is an important step to develop and test treatments as it provides researchers, clinicians, and patients with the knowledge necessary to implement specific treatments and how to alleviate symptoms. For instance, in Parkinson's disease (PD), animal models such as reserpine-treated rats and neurodegenerative models using 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mouse and 6-hydroxydopamine 6-OHDA treated rats have

been used to research various aspects of PD [15]. Animal models are essential in creating a reliable treatment as it can advance the understanding of the mechanism behind diseases and/or disorders.

Animal model studies have provided some insights into the mechanism of tremors; however, this work is limited. Current animal models used in tremor research include mice, rats, monkeys, and pigs, which are typical models for pharmacological and genetics studies [14]. An established paradigm for the preclinical evaluation of ET treatments is the harmaline-induced tremor [1], [14]. Pharmacological treatments such as propranolol, primidone, clonazepam, zonisamide, and gabapentin were found to be consistent in treating both harmaline induced animal models presenting tremors and patients with ET [1], [14]. It is important to note that there are limitations to current animal models as they cannot replicate the diverse range of symptoms that humans can present with ET. In addition, these animal models are only capable of showcasing either individual features or certain mechanisms of ET [1]. Despite decades of research, a suitable animal model for ET has not been developed. Without a suitable animal model, it remains difficult to study the inception and systemic progression of ET, as well as the exploration of possible treatments.

4 Difficulties with Diagnosis

A significant limitation with treating ET is that ET is heterogeneous in nature and comorbidities with other conditions are common. ET is diagnosed primarily on clinical symptoms according to the 2018 Consensus Statement axis 1 [1], [10]. There are no laboratory tests or neurological features that aid diagnosis, and no biomarkers or specific disease features that can be identified immediately through neuroimaging techniques [10]. ET requires at least 3 years of clinical symptoms to reduce the possibility of alternative causes of tremor, including other neurological conditions such as dystonia, and ataxia [1], [2], [16]. Up to 50% of patients with ET have been discovered to carry another diagnosis (e.g., Parkinson's disease, ataxia, dystonia, and other disorders) [1], [10]. Following an ET diagnosis, a history examination is taken, which includes information about the age of onset, symptoms of tremor, family history, any temporal evolution or exposure to tremor-inducing medication such as serotonin-reuptake inhibitors, sympathomimetic agents, lithium, and valproate, or toxins including lead, mercury, or manganese [14], [16]. The time it takes to get an accurate ET diagnosis can be detrimental by delaying the commencement of treatment.

Clinical assessments are used to pinpoint the postures and actions responsible for the activation of tremor in each patient and help distinguish ET from other movement disorders. For instance, if a patient's tremor occurs at rest, the patient will be evaluated for Parkinson's disease [16], [17]. Clinical assessments include characterizing the tremor frequency range as low (below 4Hz), medium (between 4 to 8 Hz), or high (greater than 8 Hz) to confirm the presence of pathological tremor [14]. Pathological tremors are often detected when the frequency of tremor ranges between 4-12 Hz [14], [18]. A popular test for ET patients consists of spiral drawing inspections that are used as a qualitative task for the diagnosis of ET. During this task, a patient's drawing of Archimedes spirals is captured to identify abnormal movements [9], [18]. Another assessment used is the Essential Tremor Rating Assessment Scale (TETRAS), which is an accurate and comprehensive tool used to assess the severity of ET [19]. Despite these tools and assessments, it is still a challenge to diagnose ET. For instance, as a patient ages, ET progresses, the frequency of tremor may gradually decrease, which can mimic tremors observed in Parkinson's disease [14]. This can lead to misdiagnosis and complicates the development of a treatment for ET [2], [10], [17].

An added complication of diagnosing ET is that ET is often coined "Essential Tremor Plus" or ET plus, which is ET with the presence of additional neurological symptoms and/or disorders [2]. According to the International Parkinson and Movement Disorder Society in 2017, ET and ET plus are separated in terms of diagnostic criteria [6]. ET plus involves a combination of additional neurological signs such as memory impairment, dystonia, parkinsonism, ataxia, and more [2], [6]. This adds onto the complexity of ET as it is clinically heterogeneous [20]. As mentioned above, the only tool used to assess ET is through phenotyping, which solely relies on clinical evaluations. The lack of biomarkers or defining neuropathological features used for diagnosis makes treatment difficult to develop, as ET itself is difficult to distinguish from other

disorders that have tremors as a symptom. Moreover, it is possible that ET is not a single disease but a disorder on a spectrum [20].

5 Lack of Personalized Treatments

All treatment options currently used for ET are aimed at alleviating symptoms and not preventing or treating an underlying cause. Current and experimental treatments for ET are broad and are categorized into four groups: pharmacological, Botulinum toxin (BoNT) injection, surgical, and non-invasive brain stimulations. Each has advantages and limitations with none providing a complete treatment solution for most patients.

5.1 Pharmacotherapy

Primidone, propranolol, and topiramate are the most common pharmacological treatments used to treat ET and are shown to lessen the severity of upper-limb tremor in most patients [1], [9], [16]. Approximately 30% to 70% of patients on medications find improvement in their tremors [6]. However, one-third of patients who are prescribed one of these medications stop taking them due to low tolerance of the side effects [21]. Common side effects of these drugs include asthma, heart block, bradycardia, hypotension, fatigue, weight gain, nausea, and ataxia [1]. Evidence suggests that late-onset patients find it more difficult than young-onset patients to tolerate these medications [9]. This highlights the limitation of pharmacological treatments as patients with ET often stop taking their prescribed medications due to side effects or inefficacy of the medication. Pharmaceutical treatments are limited by how much relief they can offer to symptoms. Less than half of patients find these treatments effective, and as many as 30% of patients are drug-resistant [14]. Current ET medications are repurposed from other clinical applications, further highlighting the challenge of developing a treatment that is specifically targeted at ET.

5.2 Botulinum Toxin Injection

Botulinum toxin injection (BoNT) is another common treatment to alleviate tremor in ET patients [1], [22]. BoNT is produced by *Clostridium botulinum* bacteria and related species and is a potent neurotoxin [22]. BoNT works by paralyzing specific muscles and nerves, which has the effect of decreasing the amplitude of tremors. BoNT does this by preventing the release of acetylcholine neurotransmitters from axon endings at the neuromuscular junction [1], [22]. Numerous studies have found positive outcomes with the use of BoNT for the treatment of tremor not only in ET, but in Parkinson's disease and dystonia as well [23]. BoNT is an attractive alternative treatment to patients who are drug resistant as it can be directed to the affected muscles of each ET patient. By targeting the most affected muscles, aversive side effects can be limited while providing better efficacy. However, this customized approach is quite labor intensive and requires great skills to learn the technique [23]. It is also important to note that not all ET patients respond positively to BoNT and the induced muscle weakness. Results of randomized controlled trials regarding BoNT as treatment for tremors have been inconsistent and further investigations of the long-term effects of BoNT on ET needs to be investigated [23]. Additionally, the side effects of muscle weakness are not fully understood, and it is not a reliable and long-lasting treatment option as patients need to get BoNT frequently [23].

5.3 Surgical Treatments

Surgical treatments are a second option for drug resistant ET patients with severe symptoms. Surgical procedures are invasive and have risk of adverse side effects, which can be irreversible. They can also provide life changing relief of ET symptoms. Current surgical options include deep brain stimulation and ultrasound thalamotomy [1].

Deep brain stimulation (DBS) is an invasive surgical operation that implants electrodes into the brain to electrically stimulate the intermedius ventral nucleus (VIM) of the thalamus. On average, patients find a 60% reduction in symptom severity with VIM DBS [7], [24]. The efficacy of DBS, however, reduces overtime. At 12 months post-surgery, DBS can produce 52%-66% improvement, which decreases at 2 to

3 years to 50%, and over 6 years to be 33%-48% [7]. Patients with ET often report a gradual decrease in the efficacy of DBS, which has been hypothesized to be associated with the progression of ET pathophysiology or an increase in the tolerance to the stimulation [16]. Additionally, adverse effects are common after DBS as there is a chance of stimulation-induced ataxia, tonic muscle contraction, dysarthria, disequilibrium, impaired balance, and paresthesia [16]. This adds onto the complication of why ET is so hard to treat, as DBS only alleviates symptoms to a certain degree and its efficacy decreases over time.

Ultrasound thalamotomy is another surgical treatment for ET. There are different techniques that include invasive radiofrequency, gamma knife radiosurgery, and MRI-guided focused ultrasound (MrgFUS). Each involves creating lesions to the VIM of the thalamus, contralateral to the dominant side [25]. MrgFUS thalamotomy involves a focused ultrasound to precisely destroy the VIM and it does not require cutting into the skull or brain. It has been reported to reduce tremor score by approximately 35-56% and is the most recent approved thalamotomy treatment for patients [6]. A follow-up of 4 years showed that MrgFUS resulted in improvement without any adverse events. However, there are contrasting study reports where 23% of patients expressed that their conditions worsened after the surgery at their one-year follow-ups [26]. These contradicting studies and results make it difficult to assess the success of MrgFUS. Gamma knife radiosurgery uses gamma radiation treatment to create a singular lesion in the nucleus of the VIM [7]. Compared to other surgeries, gamma knife radiosurgery takes months for effects to be noticeable. This shortcoming of gamma knife radiosurgery points to the need to better understand its effectiveness in treating tremor, as well as its risks [1], [6], [7]. These surgical options are not recommended for late-onset patients and those with comorbidities that have underlying diseases or conditions. This is due to the risk of increased complications, which can convolute the procedure and most likely result in adverse effects [6]. Furthermore, surgical treatments rarely eliminate all symptoms. This contributes to the difficulties of treating ET and how current invasive surgeries are often not the best approach.

6 Discussion

Here we reviewed the literature to better understand why essential tremor is so difficult to treat. Despite constant research to pinpoint the biomarker and mechanism of ET, the etiology and pathophysiology remain poorly understood. This lack of understanding makes the development of treatment options substantially difficult. There have been several mechanisms that have been proposed to take part in the etiology of ET such as loss of Purkinje fibres, low levels of GABA neurotransmitters, and the presence of specific genes to associate or assist in the development of ET. However, due to the complex nature of ET, no consensus has been made to prove the relevance and impact of these different mechanisms.

The lack of a suitable animal model for ET has also negatively impacted treatment development. An animal model for ET is difficult to find due to the diverse range of symptoms found in humans and the unknown and heterogeneous nature of ET [1], [14]. Current animal models are only able to either replicate a single feature of ET or a subset of its disease mechanisms [1]. Furthermore, with the lack of understanding of the mechanism of ET, it is difficult to find a suitable animal model to replicate the range of symptoms observed in humans to create an effective treatment.

Another obstacle that stands in the way of treating ET is difficulties with diagnosis due to heterogeneity and comorbidities. The signs and symptoms of ET are quite diverse and vary on a spectrum due to individual differences and comorbidities. This complicates the development of an effective treatment and/or cure that likely requires personalization to be most effective. Other than the selective injection of botulinum toxin, personalized treatments for ET are currently not available. Additionally, the only tool used to diagnose ET is phenotyping, which solely relies on clinical evaluations by visual assessments. This is important as there is no accurate or proper tool to measure and diagnose ET in patients, and it can often go misdiagnosed. For instance, ET commonly presents with other disorders such as Parkinson's disease and dystonia [10].

With the lack of personalized treatments, the diverse group of ET patients are left with generic options which are often unsatisfactory. Current treatments involve pharmacotherapy, BoNT injections, and surgical

approaches. Current medications can only reduce tremor symptoms to a certain extent and many ET patients are drug resistant. BoNT is another common treatment option; however, it is a lengthy approach as patients must regularly visit clinics for a check-up and injections every few months (typically 3 months). Surgical treatments such as DBS and thalamotomy have been utilized for severe patients. These surgeries can provide some relief but there can be adverse events due to their invasive approach. In addition, many patients find that tremors return despite undergoing surgery, and some experience negative side effects post-surgery [6]. Currently, non-invasive treatments are being investigated by clinical researchers and scientists to test whether tremors can be reduced or eliminated using tACS, transcranial magnetic stimulation or peripheral electrical stimulations [1], [6], [8], [27]. These treatment options are still experimental and require further research to provide sufficient evidence of their efficacy in treating ET. Further investigations in controlled clinical trials with large sample sizes are needed to understand why some ET patients respond better to certain treatments than others, as well as how personalized treatments can be developed. With further advancements in technology, research, and novel experimental treatments, it is promising that there may be safe and effective therapeutic options for treating ET in the near future.

7 Conclusions

ET is a common yet complex, heterogeneous movement disorder, which makes diagnosis difficult and current treatments insufficient for most patients. From this review, we draw four primary observations that help explain the current limitations of treating ET: 1) ET has unknown origin and pathophysiology, 2) there is a lack of an appropriate animal model, 3) ET is difficult to diagnose in part because of varied characteristics and comorbidities, and 4) there remains limited personalized treatments outside of invasive and often undesirable BoNT injections. A cure for ET remains elusive because an exact causal gene has not been identified, and there are no unique physiological dysfunctions in ET. The contributions of genetic and environmental factors are poorly understood, as well as the pathophysiology and etiology of ET. Animal models are necessary to develop and test novel treatments. Unfortunately, decades of research have not led to a suitable animal model for ET. There are no laboratory tests or neurological features that aid diagnosis, neither are there biomarkers or specific disease features that can be identified immediately through neuroimaging techniques. Consequently, all current treatments for ET are aimed at relieving symptoms rather than preventing or treating an underlying cause. There are many outstanding research questions that need to be addressed to improve diagnosis and treatment options for ET patients. Despite the current challenges, ET remains an active area of research, and novel experimental treatments may produce safe and effective non-invasive therapeutic options for ET.

8 Declarations

8.1 Acknowledgements

We would like to thank Dr. Michael Asmussen for thoughtful inputs to the manuscript.

8.2 Competing Interests

The authors declare no competing interests involved.

8.3 Publisher's Note

AIJR remains neutral with regard to jurisdictional claims in published institutional affiliations.

How to Cite this Article:

A. K. A. Dinh, A. J. Adeoti, and N. D. J. Strzalkowski, "Why is Essential Tremor so Difficult to Treat? A Literature Review", *Adv. J. Grad. Res.*, vol. 13, no. 1, pp. 29–36, Feb. 2023. https://doi.org/10.21467/ajgr.13.1.29-36

References

[1] T. Welton *et al.*, "Essential tremor," *Nature Reviews Disease Primers*, vol. 7, no. 1, pp. 1–17, Nov. 2021, doi: 10.1038/s41572-021-00314-w.

[2] K. P. Bhatia *et al.*, "Consensus Statement on the classification of tremors. from the task force on tremor of the International Parkinson and Movement Disorder Society," *Movement Disorders*, vol. 33, no. 1, pp. 75–87, Jan. 2018, doi: 10.1002/MDS.27121.

[3] E. D. Louis and M. McCreary, "How common is essential tremor? Update on the worldwide prevalence of essential tremor," *Tremor and Other Hyperkinetic Movements*, vol. 11, no. 1, Jul. 2021, doi: 10.5334/tohm.632.

[4] E. D. Louis and E. Louis, "The Roles of Age and Aging in Essential Tremor: An Epidemiological Perspective," *Neuroepidemiology*, vol. 52, no. 1–2, pp. 111–118, Feb. 2019, doi: 10.1159/000492831.

[5] J. S. Lou and J. Jankovic, "Essential tremor: Clinical correlates in 350 patients," *Neurology*, vol. 41, no. 2 Part 1, pp. 234–234, Feb. 1991, doi: 10.1212/WNL.41.2_PART_1.234.

[6] M. C. Sepúlveda Soto and A. Fasano, "Essential tremor: New advances," *Clin Park Relat Disord*, vol. 3, p. 100031, Jan. 2020, doi: 10.1016/J.PRDOA.2019.100031.

[7] N. I. Kremer *et al.*, "Deep Brain Stimulation for Tremor: Update on Long-Term Outcomes, Target Considerations and Future Directions," *Journal of Clinical Medicine* , vol. 10, no. 16, p. 3468, Aug. 2021, doi: 10.3390/JCM10163468.

[8] J. Frey, C. W. Hess, L. Kugler, M. Wajid, and A. Wagle Shukla, "Transcranial Magnetic Stimulation in Tremor Syndromes: Pathophysiologic Insights and Therapeutic Role," *Front Neurol*, vol. 12, p. 1482, Aug. 2021, doi: 10.3389/FNEUR.2021.700026

[9] A. Karamesinis, R. v. Sillitoe, and A. Z. Kouzani, "Wearable Peripheral Electrical Stimulation Devices for the Reduction of Essential Tremor: A Review," *IEEE Access*, vol. 9, pp. 80066–80076, 2021, doi: 10.1109/ACCESS.2021.3084819.

[10] L. N. Clark and E. D. Louis, "Essential tremor," in *Handbook of Clinical Neurology*, vol. 147, Elsevier, 2018, pp. 229–239. doi: 10.1016/B978-0-444-63233-3.00015-4.

[11] R. J. Elble, "What is essential tremor? ," *Curr Neurol Neurosci Rep*, vol. 13, no. 6, pp. 1–8, Jun. 2013, doi: 10.1007/S11910-013-0353-4

[12] E. D. Louis *et al.*, "Neuropathological changes in essential tremor: 33 cases compared with 21 controls," *Brain*, vol. 130, no. 12, pp. 3297–3307, Dec. 2007, doi: 10.1093/BRAIN/AWM266.

[13] A. M. Brown, J. J. White, M. E. van der Heijden, J. Zhou, T. Lin, and R. v. Sillitoe, "Purkinje cell misfiring generates high-amplitude action tremors that are corrected by cerebellar deep brain stimulation," *Elife*, vol. 9, Mar. 2020, doi: 10.7554/ELIFE.51928.

[14] B. Kosmowska and J. Wardas, "The Pathophysiology and Treatment of Essential Tremor: The Role of Adenosine and Dopamine Receptors in Animal Models," *Biomolecules* , vol. 11, no. 12, p. 1813, Dec. 2021, doi: 10.3390/BIOM11121813.

[15] Y. Buhidma, K. Rukavina, K. R. Chaudhuri, and S. Duty, "Potential of animal models for advancing the understanding and treatment of pain in Parkinson's disease," *n p j Parkinson's Disease* , vol. 6, no. 1, pp. 1–7, Jan. 2020, doi: 10.1038/s41531-019-0104-6.

[16] D. Haubenberger and M. Hallett, "Essential Tremor," *New England Journal of Medicine*, vol. 378, no. 19, pp. 1802–1810, May 2018, doi: 10.1056/NEJMCP1707928.

[17] M. A. Thenganatt and E. D. Louis, "Distinguishing essential tremor from Parkinson's disease: bedside tests and laboratory evaluations," *Expert Review of Neurotherapeutics* , vol. 12, no. 6, pp. 687–696, Jun. 2014, doi: 10.1586/ERN.12.49.

[18] C. Y. Kim *et al.*, "Repeated Spiral Drawings in Essential Tremor: a Possible Limb-Based Measure of Motor Learning," *The Cerebellum* , vol. 18, no. 2, pp. 178–187, Apr. 2019, doi: 10.1007/S12311-018-0974-X

[19] R. J. Elble, "The Essential Tremor Rating Assessment Scale," *J Neurol Neuromedicine*, vol. 1, no. 4, pp. 34–38, 2016, Accessed: Feb. 15, 2023. [Online]. Available: https://www.jneurology.com/articles/the-essential-tremor-rating-assessment-scale.pdf

[20] F. Holtbernd and N. J. Shah, "Imaging the Pathophysiology of Essential Tremor—A Systematic Review," *Front Neurol*, vol. 12, p. 856, Jun. 2021, doi: 10.3389/fneur.2021.680254.

[21] E. D. Louis, E. Rios, and C. Henchcliffe, "How are we doing with the treatment of essential tremor (ET)?," *Eur J Neurol*, vol. 17, no. 6, pp. 882–884, Jun. 2010, doi: 10.1111/J.1468-1331.2009.02926.X.

[22] Y. H. Liao, C. T. Hong, and T. W. Huang, "Botulinum Toxin for Essential Tremor and Hands Tremor in the Neurological Diseases: A Meta-Analysis of Randomized Controlled Trials," *Toxins (Basel)*, vol. 14, no. 3, p. 203, Mar. 2022, doi: 10.3390/TOXINS14030203.

[23] S. O. Mittal, A. Lenka, and J. Jankovic, "Botulinum toxin for the treatment of tremor," *Parkinsonism Relat Disord*, vol. 63, pp. 31–41, Jun. 2019, doi: 10.1016/j.parkreldis.2019.01.023.

[24] G. Lu *et al.*, "Outcomes and Adverse Effects of Deep Brain Stimulation on the Ventral Intermediate Nucleus in Patients with Essential Tremor," *Neural Plast*, vol. 2020, 2020, doi: 10.1155/2020/2486065.

[25] P. Wu *et al.*, "Focused Ultrasound Thalamotomy for the Treatment of Essential Tremor: A 2-Year Outcome Study of Chinese People," *Front Aging Neurosci*, vol. 13, p. 397, Jul. 2021, doi: 10.3389/FNAGI.2021.697029

[26] T. R. Wang, R. F. Dallapiazza, S. Moosa, D. Huss, B. B. Shah, and W. J. Elias, *Thalamic Deep Brain Stimulation Salvages Failed Focused Ultrasound Thalamotomy for Essential Tremor: A Case Report*, vol. 96, no. 1. Karger Publishers, 2018, pp. 60–64. doi: 10.1159/000486646.

[27] M. J. Wessel, L. R. Draaisma, and F. C. Hummel, "Mini-review: Transcranial Alternating Current Stimulation and the Cerebellum," *Cerebellum*, vol. 22, no. 1, pp. 120–128, Feb. 2022, doi: 10.1007/S12311-021-01362-4