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Essential Tremor: A Review

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Essential tremor (ET) is one of the most prevalent movement disorders globally: approximately 1% of the population is affected (Haubenberger & Hallet, 2018). In the past, ET has been grossly oversimplified clinically and pathologically and only through recent study has the complexity of the disease process and presentation been made apparent. Despite the recent advances in research regarding ET, the general public is still largely unfamiliar with the various aspects of the disease (Cristal et al., 2018). Perhaps even more surprising is the similar lack of knowledge that ET patients have regarding their own disease (Cristal et al., 2018). Recent literature on ET demonstrates an increased prevalence of previously unassociated non-motor symptoms such as depression, anxiety, apathy, dementia, and auditory deficits. These aspects of ETremain unknown among ET patients, despite their substantial effects on quality of life. Knowledge deficiencies such as these must be addressed in both clinicians and patients so as to improve the quality of life for ET patients. The following paper aims to educate the reader on the presentation, pathophysiology, progression, etiology, and treatment of ET.

Symptoms

Historically, ET has been regarded as a monosymptomatic disorder (Ashenhurst, 1973). However, recent research has demonstrated the elaborate nature of its different manifestations. Current literature on ET notes a variety of motor and nonmotor symptoms including tremors of the extremities, voice, head, as well as an increased prevalence of cognitive and psychiatric issues such as dementia, anxiety, and depression. While the prevalence of each co-symptom varies, the defining characteristic of ET remains an upper extremity tremor (Ashenhurst, 1973).

Motor

Upper extremity tremor.

The predominant clinical exhibition in ET patients is a kinetic tremor of the upper extremities (Brennan, Jurewicz, Ford, Pullman, & Louis, 2002). Kinetic tremor may occur with multiple voluntary movements such as eating, drinking, writing, and many other activities of daily living (Louis, 2005). A postural tremor of the arms is another common component of ET; however, it typically demonstrates a lower severity relative to kinetic tremor (Brennan et al., 2002). Deuschl, Raethjen, Hellriegel, and Elble (2000) suggests that intention tremor should be included in the clinical definition of ET in conjunction with postural tremor, despite similar clinical presentations. Cohen, Pullman, Jurewicz, Watner, and Louis (2003) and Rajput, Rozdilsky, Ang, and Rajput (1993) provide evidence for rest tremor, distinct from Parkinson's Disease, in 20-33% of ET patients. While the significance of rest tremor in ET is still unknown, its presence in ET cases is associated with increased severity and longer duration of other ET symptoms (Cohen et al., 2003). Hubble, Busenbark, Pahwa, Lyons, and Koller (1997) demonstrated that men with ET often present with an increased severity of postural hand tremor; women with ET demonstrated a greater prevalence (>60%) of head and voice tremor than men (~30%). The differentiation of symptom variance between sexes is important for accurate clinical diagnosis; thus the differences noted in men and women regarding the prevalence of ET symptoms are noteworthy.

Additional tremor loci.

Although ET primarily exhibits symptoms in the arms, it may also manifest as a tremor of the head, voice, trunk, legs, and other facial musculature as noted by Critchley (1949).

Prevalence of dual head (neck) and arm tremor among ET cases tends to fall between 34-53% depending on the study sample (Louis, 2005), while isolated head tremor occurs in less than 10% of ET cases (Louis, Ford, & Frucht, 2003). Approximately 75% of head tremor cases take the form of a "no-no" variety (Bain et al., 1994). Tandem gait abnormalities have also been noted in 50% of ET patients aged >70 years with a 2-fold increase in risk of abnormal gait development as compared to a healthy elderly population (Singer, Sanchez-Ramos, & Weiner, 1994). The extensive, inconsistent nature of ET motor symptoms is only further complicated by the variety of non-motor symptoms that may be present as well.

Non-motor

Auditory and olfactory.

An association between ET and auditory and olfactory deficits has been demonstrated (Sengul, 2020). Hearing loss and neurodegenerative disease processes often go hand in hand. Two studies have reported significant association between ET and hearing impairment as well as an increased prevalence of impairment in ET as compared to other neurodegenerative conditions such as Parkinson's Disease (Ghika, Kyrozis, Potagas, & Louis, 2015; Sengul, 2020). While these discoveries are helpful, further research must be completed to illuminate the nature of this association. Reports regarding a positive relationship between olfactory deficits and ET are conflicting, primarily demonstrating that further research must be accomplished prior to the development of any concrete assumptions (Louis, 2016).

Cognitive and psychiatric.

An increased prevalence of several cognitive and psychiatric features have been noted among ET patients as well (Louis, 2016). ET patients have demonstrated mild cognitive

impairment greater than age-matched controls (Lacritz, Dewey, Giller, & Cullum, 2002). This impairment primarily involves executive function and memory and appears to be progressive (Louis, 2016). An increased prevalence of dementia has also been noted among ET cases (Janicki, Cosentino, & Louis, 2013). ET patients also demonstrate a greater amount of depressive symptoms than controls (Louis, 2016). Dogu, Louis, Sevim, Kaleagasi, & Aral (2005) demonstrated that increased depression scores correlated with an increase in tremor severity among ET patients. Within ET patients, those with a head tremor demonstrate a higher prevalence of depression and memory deficiencies (Peng et al., 2020).

There is a dearth of research regarding the presence of apathy in ET patients. However, one study noted an increase in apathy among non-depressed ET cases as compared to controls (Louis, Huey, Gerbin, & Viner, 2012). This is notable due to the increased presence of apathy noted among other movement disorders such as Parkinson's Disease (35%) (Santangelo et al., 2013). Despite the poorly documented nature of apathy in ET, multiple studies have reported a substantially increased incidence of anxiety among ET patients (Sengul et al., 2014; Chandran et al., 2012) paired with an increased acuity of anxiety as compared to controls (Dogu et al., 2005). ET patients have specifically demonstrated a higher rate of social phobia compared to controls (Schneier, Barnes, Albert, & Louis, 2001). The prevalence of anxiety among ET patients was shown to still be greater even in patients with mild ET who had not been previously diagnosed (Dogu et al., 2005). This is noteworthy because it demonstrates an increased prevalence of anxiety that is not developed in response to diagnosis or severe symptoms, but appears to be tied directly to the disease process itself.

Alexithymia—the inability to identify and describe experienced emotions—has recently been demonstrated to appear at significantly higher rates in ET patients than controls, even independent of depressive symptoms (Sengul et al., 2020). While further research must be performed to further demonstrate the clinical applicability of this study, alexithymia has been noted to appear with increased prevalence in Parkinson's Disease and thus it is not particularly surprising that it is prevalent in ET given the many similarities between the two diseases (Assogna et al., 2012). ET patients may also demonstrate an impaired quality of sleep (Jimenez-Jimenez, Alonso-Navarro, Garcia-Martin, & Agundez, 2020; Peng et al., 2020); however, Sengul et al., (2014) noted that sleep deficits in ET were associated with elevated anxiety levels and were therefore a better marker of anxiety incidence in ET than a purely unrelated sleep impairment.

Elbelkemy, Shalash, Mansour, Hamed, and Abdelalim (2020) argued that as non-motor symptoms in ET are increasingly evident, they should be included in the clinical definition of ET. However, it is as yet unclear whether these non-motor symptoms are a significant part of the primary disease process, or whether they are primarily secondary reactive symptoms of ET (Jhunjhunwala & Pal, 2014). While this distinction is currently unclear, it is quite apparent that ET patients exhibit a high frequency of neuropsychiatric deficits and experience a lower quality of life due to these deficits (Lorenz, Poremba, Papengut, Schreiber, & Deuschl, 2011; Mussachio et al., 2016). Therefore, clinicians should anticipate, educate, and treat ET patients for non-motor symptoms so as to ensure a higher quality of life. Interestingly, non-motor symptoms appear to be independent of tremor severity, further supporting their inclusion as a primary ET component rather than a reactive component (Louis et al., 2001; Mussachio et al., 2016). The

increasingly realized prevalence and severity of non-motor symptoms in ET further potentiates the inclusion of non-motor symptoms as a primary disease process of what was once thought to be a monosymptomatic tremor disorder.

Pathophysiology

The pathophysiology of ET is likely multifactorial and is not fully understood. Research has only further demonstrated the intricacy of the disease pathology and the necessity for further investigation on the topic. The post-mortem nature of ET biological research constitutes a primary barrier to the attainment of concrete evidence surrounding its cause. However, the subject has received increasing attention over the past 15 years and much has been gained regarding the pathophysiology of ET. Currently, ET pathology is largely considered to be a primary neurodegenerative disorder of the cerebellar cortex (Bares, Husarova, & Lungu, 2001; Cerasa & Quattrone, 2016; Louis, 2014).

Purkinje Cell Degeneration

One theory regarding the pathophysiology of essential tremor suggests that it is due to a progressive degeneration of Purkinje neurons (Grimaldi & Manto, 2013) of the cerebellum. In ET patients, Purkinje cell production of Gamma-aminobutyric acid (GABA) subsequently decreases along with the inhibitory effect on cerebellar nuclei for which GABA is produced (Grimaldi & Manto, 2013). The Purkinje cells in ET undergo a certain degree of degeneration which includes the development of axonal swelling (torpedoes) and reduction in dendritic cell complexity (Louis, 2014). This reduction in dendritic arborization is thought to precede cell death which may explain the lower Purkinje cell counts noted in ET (Ferrer, Fabregues, Pineda, Gracia, & Ribalta, 1984; Grimaldi & Manto, 2013). Louis et al. (2014) demonstrated that with an

increased exhibition of tremor severity, a decrease in dendritic arborization was also present; this association provides further evidence for the direct role of Purkinje cell degeneration in exhibition of ET symptoms.

Lin et al. (2014) established that a decrease in climbing fibre-Purkinje synapse connection was evident in ET cases. Basket cells adjacent to Purkinje cells have also demonstrated some extent of remodeling, further exemplifying the involvement of neighboring processes. (Louis, 2014). Multiple Purkinje axonal irregularities—torpedoes, axonal atrophy, increased collateralization, branching, and sprouting—are markedly increased in ET cases as opposed to controls (Babij et al., 2013). Prior research has demonstrated that these Purkinje cell abnormalities are compensatory in nature and a result of physiologic stress (Ramon y Cajal, 1928); these compensations would thus attempt to sustain connections despite the stress induced by ET (Babij et al., 2013). Choe et al. (2016) suggest that the degeneration of Purkinje cells and neighboring processes is likely due to an unknown molecular abnormality in ET patients which could simply label Purkinje cell deviations as biomarkers resulting from a deeper cellular pathology. Overall, it is still unclear whether Purkinje cell aberrations noted are a result of essential tremor or simply indicate a greater predisposition to tremor development.

Louis (2014) proposed a model of cerebellar degeneration in ET. This model suggests that an underlying molecular event of unknown origin results in Purkinje axonal remodeling, selective cell death, adjacent processes remodeling, aberrant synapse formation, and an overall abnormal Purkinje cell and corticofugal output (Louis, 2014). This cascading process details the potential regenerative and degenerative modifications that occur in Purkinje cell-connected populations, largely resulting in a rewiring of the cerebellar circuitry. A model such as this

suggests that the neurodegenerative nature of ET elicits a modification of cerebellar circuitry and thus the symptoms of ET begin. Despite the substantial quantity of evidence regarding Purkinje cell abnormalities and loss, there is contradicting research that reports no difference in Purkinje cell loss between ET cases and controls (Rajput, Robinson, Rajput, Robinson, & Rajput, 2012). This only further exemplifies the need for further research to clarify the relationship between Purkinje cells and ET. Overall, it is likely that the aberrations noted in Purkinje cells and their neighboring processes play a significant role in the pathology of ET due to the considerable data presented in the previously mentioned studies.

GABA Receptor Reduction

The GABAergic nature of Purkinje cells and their involvement in ET pathology provides insight into the essential query of an isolated study regarding the reduction of GABA receptors in ET. Paris-Robidas et al. (2012) recorded a significant decrease in dentate nucleus GABA receptors among ET patients. An inverse relationship between GABA receptor concentration and duration of essential tremor was also noted (Paris-Robidas et al., 2012). The researchers theorize that a reduction in GABA receptors within the dentate nucleus produces a disinhibition of deep cerebellar pacemaker output; this propagates along the cerebello-thalamo-cortical pathways to induce tremors (Paris-Robida et al., 2012); this is further demonstrated by a decrease of GABA in the cerebrospinal fluid of ET cases (Mally & Baranyi, 1994; Mally, Baranyi, & Vizi, 1996). Despite the relative uncertainty of the precise role that GABA and its receptors have in ET, it is clear that they represent an integral component of understanding the disease process.

Insoluble Protein Accumulation

One study noted that ET case levels of insoluble Amyloid beta in the cerebellar cortex were substantially higher than controls (Béliveau et al., 2015). An increase in insoluble Amyloid beta 42 was also discovered in the cerebral parietal cortex of all ET cases and the cerebellar white matter of the majority of ET cases, a primary indication of widespread amyloidosis (Béliveau et al., 2015). This is significant due to the central, although somewhat unclear, role of amyloid-beta plaque accumulation in Alzheimer's Disease cases (Bourdenx et al., 2017). Béliveau et al., (2015) also demonstrated that high levels of Amyloid beta 42 in ET cases correlated with excessive amounts of insoluble phosphorylated tau, unphosphorylated Neurofilament-H (NF-H) and Leucine rich repeat and immunoglobulin domain-containing Nogo receptor-interacting protein 1 (LINGO1), suggestive of generalized cerebellar neurodegeneration. Elevated cerebellar LINGO1 in ET is consistent with previous research and may be found in Parkinson's Disease cases as well; however, it is only reported in ET duration of greater than 20 years (Delay et al., 2014). Likewise, phosphorylated and unphosphorylated NF-H have been demonstrated at elevated concentrations in ET cases (Louis et al., 2012). Significant lewy body accumulation has also been recorded in the locus coeruleus of ET cases, providing further evidence of similarities between ET and Parkinson's Disease (Louis, 2010). It is unclear whether the accumulation of these proteins constitutes a portion of the primary disease process or whether they are simply biomarkers. Despite this relative uncertainty, they are regarded as an important facet of cellular disruption in several neurodegenerative diseases and therefore these findings are quite substantial. While more research must be performed on the prevalence and implications of protein aggregation in the ET cerebellum and adjacent structures, the current

literature supports the concept of ET as a primary, neurodegenerative disease process of the cerebellum.

White and Grey Matter Deterioration

Ultrastructural white matter bundle alterations have been noted in ET (Nestrasil et al., 2018; Pietracupa et al., 2019). Most notably, white matter abnormalities were discovered in the corpus callosum, corticospinal tracts, superior longitudinal fasciculi, and cerebellar peduncle; aberrations in these areas were significantly correlated with tremor severity (Pietracupa et al., 2019; Prasad, Pandey, Saini, Ingalhalikar, & Pal, 2019). It must, however, be noted that there is currently contradiction in the literature regarding correlations between tremor severity and white matter alterations in ET (Nestrasil et al., 2018) and thus there is no resolution in this matter. Grey matter damage has likewise been noted but research is inconsistent on its distribution—isolated thalamic depreciation (Pietracupa et al., 2019) as opposed to significant atrophy of the cerebellum (Prasad et al., 2019). Thalamic deterioration demonstrates a strong correlation with the presence of minor cognitive impairment, a notable non-motor symptom of ET (Pietracupa et al., 2019). Deterioration of grey matter in the thalamus and white matter of the superior cerebellar peduncles remains consistent with the previously mentioned hypothesis of cerebello-thalamo-cortical circuit dysfunction in ET and agrees with earlier research regarding the integral role of this circuit in ET pathology (Hallet, 2014). However, the widespread nature of the white matter aberrations suggests that ET pathology involves multiple brain structures, not simply degeneration of cerebellar processes, while also supporting the concept of ET as a neurodegenerative disorder. Research regarding widespread atrophy of the cerebellum and cerebellar peduncles in ET provides evidence of macrostructural integrity changes and thus

potential for future use of Magnetic Resonance Imaging as aid in diagnosis of the disease (Cao et al., 2018; Mavroudis, Petridis, & Kazis, 2019; Prasad et al., 2019).

Much research has recently been performed regarding the heterogeneous pathophysiology of ET. The diverse, occasionally conflicting and somewhat erratic results provide reason to question the identity of ET as a single entity. Rather, it is quite possible that it may in fact be a family of diseases or "the essential tremors" as put by Louis (2013). Multiple pathological entities have been described potentiating the distinction of certain anatomical features in ET description such as a cerebellar ET (Louis, 2009). Potential for subsets of ET have also been noted such as the increase in non-motor symptoms associated with midline tremor in ET (Huang et al., 2020). While this does raise concerns for future diagnosis and research—specifically the manner in which case subjects are selected—of ET, it primarily further exemplifies the profound need for distinctive, collaborative research.

Recent literature suggests a degenerative cascade, similar to the model referenced earlier from Louis (2014). This putative degenerative cascade would progress from Purkinje axonal swelling, basket cell remodeling, and the loss of GABA receptors to ultimately culminate in a reduction of GABAergic tone (Louis & Faust, 2020). Diminution of GABAergic tone would result in a hyperexcitable state that may produce a tremor. This theory would explain the pathology of ET and potentiate discernment between primary degenerative aspects and successive compensatory developments to try and restore GABAergic tone. Additional research must be performed in order to better support this theory and provide further detail as to the pathophysiology of ET.

Progression

The neurodegenerative nature of ET is further supported by the progressive fashion in which the disease presents—notably its insidious onset, gradual progression, and increased incidence in older populations (Louis et al., 2017). There is, however, a paucity of longitudinal research following ET patients and the severity of their symptoms; this makes it extremely difficult to quantify the rate of progression in ET. Despite the current lack of significant longitudinal data, several studies have demonstrated a progressive decline in ET patients over follow-ups of 3-6 years (Gironell, Ribosa-Nogué, Gich, Marin-Lahoz, & Pascual-Sedano, 2015; Louis, Agnew, Gillman, Gerbin & Viner, 2011; Putzke, Whaley, Baba, Wszolek, & Uitti, 2006). Gironell et al., (2015) noted a relationship between age of disease onset and the rate of progression; they hypothesized that the rate of progression is low when tremor symptoms are noted prior to the age of 40 years. In contrast, Louis et al. (2017) noted a rapid rate of progression in older-onset ET; an increased age of onset was also associated with an increase in degenerative pathology. However, Kuo et al., (2017) noted no significant difference in cerebellar pathology between early and late onset ET. Louis et al. (2017) further demonstrated no significant differences in cerebellar pathology between familial and sporadic ET; this supports the previous study due to the early nature of familial ET onset. Overall, there is much to be learned about the progression of ET and further research is needed to clarify the relationship between progression and other factors such as age of onset. However, it is likely that progression rate differs considerably with varying ages of onset and thus some comfort may be provided for patients with early onset ET.

Etiology

Genetic Factors

There are several factors which appear to influence the likelihood of ET development. Genetic factors play an important role as ET often presents in a familial fashion and risk of ET development increases substantially for patients with affected family members. Louis et al. (2001) demonstrated that the risk of developing ET is five times greater for first-degree relatives of ET patients and ten times greater if the relative developed the tremor at an early age. Indeed, familial tremor constitutes 50-70% of ET cases (Sullivan, Hauser, & Zesiewicz, 2004). Recent genetic analyses have recorded 14 loci and 11 genes—notably, mutations in the LINGO1 gene (Stefansson et al., 2009)—with some relation to ET (Deng, Wu, & Jankovic, 2019). LINGO1 gene variants in ET potentiates a connection to the increased levels of LINGO1 noted in ET cases and suggests the need for research to determine any association between the two. Despite recent discoveries in ET genetics, no causative genes for ET have been identified. This suggests a complex combination of genetic factors that likely interact with the environment in the development of ET pathology.

Environmental Factors

Diet.

Environmental factors have constituted a significant portion of the ET discussion for quite some time, although there are varying reports regarding the nature of these factors. The effects of diet, smoking, and occupational toxin exposure have been examined for their relation to ET (Ong, Deng, & Tan, 2019). β-carboline alkaloids are a well-known neurotoxin and have demonstrated tremor-inducing effects when administered to both laboratory animals and humans

(Louis & Zheng, 2010). ET cases have demonstrated elevated levels of harmane, a β-carboline alkaloid, as compared to healthy controls (Louis et al., 2002; Louis et al., 2008). An association between higher harmane levels and increased severity of ET has also been reported, further demonstrating the possible role of elevated harmane in ET (Louis et al., 2008). Harmane is found in meat-products and is ingested in higher concentrations than it is endogenously created (Ong et al., 2019). Despite this, ET patients have demonstrated no significant differences in animal protein intake when compared with controls and no correlation has been found between intake and Harmane levels (Louis, Zheng, Applegate et al., 2005). This suggests that dietary intake of Harmane is not an adequate measure of the risk of ET development or aggravation, although further research is necessary to make any entirely conclusive statements on the subject. Altogether, elevated harmane levels appear to play some role in ET development and severity, despite the unclear nature of their increase.

Historically, alcohol has been regarded as a potentially protective factor due to its transient reduction of tremor severity upon intake (Ong et al., 2019). However, ethanol is a well-established cerebellar toxin and may illicit degenerative effects such as Purkinje cell loss and cerebellar atrophy, as is also noted in ET pathology (Anderson, 2004; Dlugos, 2008; Yokota et al., 2007). Despite this degradory effect, no significant association has been found between ET and alcohol intake (Jimenez-Jimenez et al., 2007; Louis et al., 2004). Additionally, no correlation is noted between average alcohol intake and tremor severity, further highlighting the transient nature of alcohol's suppression of tremor (Louis & Michalec, 2014). Louis, Benito-Leon, and Bermejo-Pareja (2008) did find a minor association between alcohol intake and risk of ET development; in the study, the highest quartile of alcohol consumers—drinking an average of 3-4

standard drinks per day—demonstrated twice the risk of ET development. While this study is rather isolated, it demonstrates a dire need for more research on the long-term effects of alcohol on ET. Interestingly, a small Italian study recorded a negative correlation between wine consumption and ET development, potentially due to the significant antioxidant properties of wine (Nicoletti et al., 2011). Antioxidants have briefly been examined as a potential protective factor. While no difference in intake of individual antioxidants such as vitamins C and E has been found with ET patients (Louis, Jurewicz, & Parides, 2005), adherence to the Mediterannean diet was inversely correlated with risk of ET development (Scarmeas & Louis, 2007). The antioxidant-rich nature of the Mediterannean diet suggests a potential protective intervention that may be made to decrease the risk of ET development. Notable aspects of the Mediterannean diet also include decreased red meat intake and consumption of red wine in moderation, perhaps demonstrating a broader coalition of protective interventions rather than just an increase in overall antioxidant intake. While caffeine consumption was previously thought to increase tremor severity, no correlation has been found between caffeine intake and the severity or duration of ET symptoms (Nicoletti et al., 2011; Louis et al., 2004; Prakash, Choong, Yuen, & Tan, 2006). Overall, the effects of diet on ET development and severity are not concretely evident and further research is needed to examine the relationship between factors such as meat intake and Harmane levels. However, current literature suggests that dietary interventions such as a decrease in overall alcohol intake and adherence to the Mediterannean diet may decrease the risk of ET development.

Occupational exposure.

Several habitual and occupational hazards have also been noted as having some affect on ET. While smoking is often regarded as a detrimental health habit, Benito-Leon, Louis, and Bermejo‐Pareja (2008) demonstrated an inverse relationship between smoking and risk of ET; indeed, the highest pack per year group had ⅓ the risk of ET development as compared to never-smokers. This is not entirely surprising as nicotine appears to provide some protection from neurotoxic detriments (Picciotto & Zoli, 2008; Quick, Perez & Bordia, 2012; Shimohama, 2008). While the nicotine content received with smoking may provide some protective elements against ET development, it is certainly not clinically recommended due to the significant health detriments associated with chronic exposure to smoke. A positive association between pesticide exposure and ET has also been noted (Azevedo & Meyer, 2017; Yao, Wang, & Yang, 2014). However, other studies have demonstrated a complete lack of association between the two and thus more research is required to further illuminate the potential effects of pesticide exposure on the development of ET (Jimenez-Jimenez et al., 2007; Louis, Factor-Litvak, et al., 2006; Prakash, Choong, Yuen, & Tan, 2006). ET cases have also demonstrated a higher level of blood lead concentrations as compared to controls (Dogu et al., 2007; Louis et al., 2003). This is significant due to the destructive nature of lead on cerebellar tissue and Purkinje cells, as is noted in ET pathology (Ong et al., 2017).

The conflicting results of the relationship between ET and occupational exposure provides significant difficulties in the navigation of ET risk factors. While smoking likely decreases the risk of ET development, it is not an appropriate intervention due to its other well-known health detriments. The role of pesticide exposure in ET is grossly unclear and further

research is required to provide any clinical recommendations. Overall, while much research is still required to further clarify the etiology of ET, it is likely that a complex relationship between genes and environment exists and dictates the development of ET as multiple factors of both parties have proven significant in their affiliation with ET.

Treatment

Although ET is not often regarded as debilitating, several treatments have been explored and further innovations and research are providing greater potential for complex treatment approaches to match an ever-growing knowledge of the extent and complexity of ET. Currently, all treatments are directed at symptom reprief and do not aim to impact ET development or progression pathologically.

Pharmacological Interventions

Historically, Propranolol and Primidone have been the primary medications prescribed in treatment of ET symptoms (Zesiewicz et al., 2011). Propranolol and Primidone have been demonstrated to reduce tremor for at least one year (Findley, Cleeves, Calzetti, 1985; Murray, 1976; Paparella et al., 2018; Sasso, Perucca, Fava, & Calzetti, 1990; Winkler & Young, 1974). However, no longitudinal studies have been performed regarding the long-term efficacy of Propranolol and Primidone. Primidone decreases tremor severity noticeably earlier than Propranolol, but both have the same overall outcome (Dietrichson & Espen, 1987). While each medication has independently demonstrated effective reduction in extremity tremor severity, dual therapy provides the greatest level of tremor reduction in 30-70% of patients; however, the overall result is rather modest (Bain, 1997; Schaefer, Rodriguez, & Louis, 2017). In addition, up to ⅓ of patients develop pharmacoresistance (Deuschl, Raethjen, Hellriegel, & Elble, 2011) and

discontinue their medication due to undesirable side effects and lack of satisfactory tremor resolution (Louis, Rios, & Henchcliffe, 2010). In the event that Propranolol is contraindicated for a patient, Metoprolol may be substituted and demonstrates similar efficacy (Calzetti, Findley, Gresty, Perucca, & Richens, 1981; Calzetti, Findley, Perucca, & Richens, 1982). However, other beta-blockers demonstrate inconsistent or less effective results when used to treat ET (Calzetti et al., 1981). Topiramate may also be prescribed for moderate to severe ET, although it is less effective than the combination therapy of Primidone and Propranolol (Connor & Edwards, 2008; Ferreira et al., 2019; Ondo et al., 2006; Schaefer, Rodriguez, & Louis, 2017). Some research has demonstrated a possible use for botulinum neurotoxin injection in reduction of tremor severity (Ferreira et al., 2019). While other medication regimes target extremity tremors of the disease, use of botulinum toxin type A has exhibited significant improvement in head and voice tremor (Adler et al., 2004; Gurey, Sinclair, & Blitzer, 2013; Guglielmino, Moraes, Villanova, Padovani, & Biase, 2018; Hertegård, Granqvist, & Lindestad, 2000; Pahwa et al., 1995; Warrick et al., 2009; Wissel, Masuhr, Schelosky, Ebersbach, & Poewe, 2004). Nonetheless, additional research is required to ensure the appropriateness of botulinum administration for ET. Pharmacological interventions appear to primarily provide transient relief and other interventions must be sought out for long-term treatment of ET symptoms.

Surgical Interventions

Several other treatment methods for ET exist, one of which is Deep Brain Stimulation (DBS) of the ventralis intermedius nucleus of the thalamus. DBS has proven effective for at least one year post-operation (Borretzen et al., 2014; Koller et al., 1997; Koller, Lyons, Wilkinson, Troster, & Pahwa, 2001; Pahwa et al., 2001). However, Borretzen et al. (2014) noted that up to

40% of patients develop a tolerance and thus efficacy of DBS significantly decreases over time. Additional studies displayed a 73% reduction in long-term efficacy of DBS (Wang et al., 2018; Sandoe et al., 2013). Despite the unfortunate decrease in desirable outcome duration, DBS demonstrates up to a 90% reduction in tremor severity and consequently an increase in overall functionality (Nazzarro, Lyons, & Pahwa, 2013). Bilateral DBS has been noted to be more effective than a unilateral approach (Pahwa et al., 2006). Unfortunately, bilateral procedures are associated with an increase in adverse side effects, such as gait disturbances and dysarthria, when compared to unilateral DBS (Nazzarro, Lyons, & Pahwa, 2013).

A thalamotomy may also be performed to reduce severe tremors in ET. A similar efficacy has been demonstrated between unilateral DBS and thalamotomy—up to 90% effective in suppression of limb tremor (Giordano et al., 2020; Jankovic, Cardoso, Grossman, & Hamilton, 1995; Kim et al., 2017; Tasker et al., 1997; Park, Jung, Na, & Chang, 2019; Witjas et al., 2015; Zirh, Reich, Dougherty, & Lenz, 1999). However, bilateral DBS shows the greatest improvement of tremor severity overall (Giordano et al., 2020). There is minor evidence that non-invasive brain stimulation, primarily of the cerebellar and motor cortical regions, has a positive affect on tremor severity (Chalah, Lefaucheur, & Ayache, 2015; Kang & Cauraugh, 2017). However, further research is needed to confirm the veracity of these results. Altogether, surgical interventions for ET appear to provide the greatest relief of symptoms, but they mimic the pharmacological interventions in the transiency of their effects.

Alternative Interventions

Several innovative studies have sought to measure the potential of supportive exoskeletons or “orthoses" for non-pharmacological treatment of ET. Multiple studies have

demonstrated a significant reduction in tremor amplitude and occurrence with the application of orthoses (Herrnstadt, McKeown, & Menon, 2016; Herrnstadt & Menon, 2019; Loureiro et al., 2005). One study even demonstrated a 98% reduction in tremor with use of the orthosis (Rocon et al., 2007). Despite these impressive results, the devices were not tolerated well and patients complained of the bulky nature of the instruments (Castrillo-Fraile et al., 2019). A multichannel stimulator utilizing asynchronous electrode activation has also been developed and demonstrates a decrease in tremor amplitude of up to 80% (Maneski et al., 2011).

Alternative medicine therapies have also been briefly explored. Kang et al. (2020) recorded that 70% of ET patients who used Korean herbal medicine reported that it was highly effective at treating their tremor symptoms. While this demonstrates some potential for herbal treatment, it is difficult to assess the true validity of these results as the data was self-reported by patients. While orthoses and other innovations seem to provide substantial relief in ET symptom severity, they do not appear to be feasible for everyday use due to their cumbersome nature. Overall, it is clear that extensive research must be performed in order to better develop and evaluate treatment options for ET.

Conclusion

Despite considerable research efforts over recent years, ET remains relatively unclear in its pathophysiology, inconsistent in its presentation, and considerably uncertain in its etiology. Treatment methods show promising results, but they rapidly decrease therapeutically or are impractical for everyday activities. Significant research must continue so as to refine current theories, distinguish the cause of symptom anomalies, enrich our etiological knowledge, and provide additional therapies for patients. Although much is still unknown, the substantial

advance in ET literature over the past 15 years is encouraging and provides hope for rapid accumulation of disease knowledge in the future.

References

Adler, C. H., Bansberg, S. F., Hentz, J. G., Ramig, L. O., Buder, E. H., Witt, K., ... Caviness, J. N. (2004). Botulinum toxin type A for treating voice tremor. *Archives of Neurology, 61*, 1416-1420. doi:10.1001/archneur.61.9.1416

Andersen, B. B. (2004). Reduction of Purkinje cell volume in cerebellum of alcoholics. *Brain Research*, *1007*, 10–18. doi:10.1016/j.brainres.2004.01.058

Ashenhurst, E. M. (1973). The nature of essential tremor. *Canadian Medical Association Journal, 109*, 876–878.

Assogna, F., Palmer, K., Pontieri, F. E., Pierantozzi, M., Stefani, A., . . . Spalletta, G. (2012). Alexithymia is a non-motor symptom of Parkinson disease. *The American Journal of Geriatric Psychiatry, 20*(2), 133-141. doi:10.1097/JGP.0b013e318209de07

Azevedo, M. F. A., & Meyer, A. (2017). Essential tremor in endemic disease control agents exposed to pesticides: A case‐control study. *Cadernos de Saude Publica, 33*(8), e00194915. doi:10.1590/0102-311X00194915

Babij, R., Lee, M., Cortés, E., Vonsattel, J. P., Faust, P. L., & Louis, E. D. (2013). Purkinje cell axonal anatomy: Quantifying morphometric changes in essential tremor versus control brains. *Brain, 136*, 3051–3061. doi:10.1093/brain/awt238

Bain, P. G., Findley, L. J., Thompson, P. D., Gresty, M. A., Rothwell, J. C., Harding, A. E., & Marsden, C. D. (1994). A study of hereditary essential tremor. *Brain, 117*, 805–824. doi:10.1093/brain/117.4.805

Bain, P. G. (1997). The effectiveness of treatments for essential tremor. *The Neurologist, 3*,

305–321. Retrieved from https://journals.lww.com/theneurologist/abstract/1997/09000/the_effectiveness_of_treatments_for_essential.3.aspx

Bares, M., Husarova, I., & Lungu, O. V. (2012). Essential tremor, the cerebellum, and motor timing: Towards integrating them into one complex entity. *Tremor and Other Hyperkinetic Movements, 2*. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3572554/

Béliveau. E., Tremblay, C., Aubry-Lafontaine, É., Paris-Robidas, S., Delay, C., Robinson, C., … Calon, F. (2015). Accumulation of amyloid-β in the cerebellar cortex of essential tremor patients. *Neurobiological Disorders, 82*, 397-408. doi:10.1016/j.nbd.2015.07.016

Benito‐Leon, J., Louis, E. D., & Bermejo‐Pareja, F. (2008). Population‐based case‐control study of cigarette smoking and essential tremor. *Movement Disorders, 23*(2), 246– 252. doi:10.1002/mds.21810

Børretzen, M. N., Bjerknes, S., Sæhle, T., Skjelland, M., Skogseid, I. M., Toft, M., & Dietrichs, E. (2014). Long-term follow-up of thalamic deep brain stimulation for essential tremor – patient satisfaction and mortality. BMC Neurology, 14(1), 120-120. doi:10.1186/1471-2377-14-120

Bourdenx, M., Koulakiotis, N. S., Sanoudou, D., Bezard, E., Dehay, B., & Tsarbopoulos, A. (2017). Protein aggregation and neurodegeneration in prototypical neurodegenerative diseases: Examples of amyloidopathies, tauopathies and synucleinopathies. *Progress in Neurobiology, 155*, 171-193. doi:10.1016/j.pneurobio.2015.07.003

Brennan, K. C., Jurewicz, E. C., Ford, B., Pullman, S. L., & Louis, E. D. (2002). Is essential

tremor predominantly a kinetic or a postural tremor? A clinical and electrophysiological study. *Movement Disorder, 17*(2), 313–16. doi:10.1002/mds.10003

Calzetti, S., Findley, L. J., Gresty, M. A., Perucca, E., & Richens, A. (1981). Metoprolol and propranolol in essential tremor: a double-blind, controlled study. *Journal of neurology, neurosurgery, and psychiatry*, *44*, 814–819. doi:10.1136/jnnp.44.9.814

Calzetti, S., Findley, L. J., Perucca, E., & Richens, A. (1982). Controlled study of metoprolol and propranolol during prolonged administration in patients with essential tremor. *Journal of neurology, neurosurgery, and psychiatry*, *45*, 893–897. doi:10.1136/jnnp.45.10.893

Cao, H., Wang, R., Luo, X., Li, X., Hallett, M., Thompson-Westra, J., . . . Yang, X. (2018). A voxel-based magnetic resonance imaging morphometric study of cerebral and cerebellar gray matter in patients under 65 years with essential tremor. *Medical Science Monitor, 24*, 3127-3135. doi:10.12659/msm.906437

Castrillo-Fraile, V., Peña, E. C., Gabriel Y Galán, J. M. T., Delgado-López, P. D., Collazo, C., & Cubo, E. (2019). Tremor control devices for essential tremor: A systematic literature review. *Tremor and Other Hyperkinetic Movements, 9*, 1-6. doi:10.7916/tohm.v0.688

Cerasa, A. & Quattrone, A. (2015). Linking essential tremor to the cerebellum—neuroimaging evidence. *The Cerebellum, 15*(3), 263-275. doi:10.1007/s12311-015-0739-8

Chalah, M. A., Lefaucheur, J. P., & Ayache, S. S. (2015). Non-invasive central and peripheral stimulation: New hope for essential tremor?. *Frontiers in Neuroscience*, *9*, 440. doi:10.3389/fnins.2015.00440

Chandran, V., Pal, P. K., Reddy, J. Y., Thennarasu, K., Yadav, R., & Shivashankar, N. (2012). Nonmotor features in essential tremor. *Acta Neurologica Scandinavica, 125*(5), 332–337.

doi:10.1111/j.1600-0404.2011.01573.x

Choe, M., Cortés, E., Vonsattel, J. P., Kuo, S. H., Faust, P. L., & Louis, E. D. (2016). Purkinje cell loss in essential tremor: Random sampling quantification and nearest neighbor analysis. *Movement disorders, 31*(3), 393–401. doi:10.1002/mds.26490

Cristal, A. D., Chen, K. P., Hernandez, N. C., Factor-Litvak, P., Clark, L. N., Ottman, R., & Louis, E. D. (2018). Knowledge about essential tremor: A study of essential tremor families. *Frontiers in Neurology, 9*(27). doi:10.3389/fneur.2018.00027

Critchley, M. (1949). Observations on essential tremor (heredofamilial tremor). *Brain, 72*(2), 113–139. doi:10.1093/brain/72.2.113

Cohen, O., Pullman, S., Jurewicz, E., Watner, D., & Louis, E. D. (2003). Rest tremor in essential tremor patients: Prevalence, clinical correlates, and electrophysiological characteristics. *Archives of Neurology, 60*(3), 405–410. doi:10.1001/archneur.60.3.405.

Connor, G. S., Edwards, K., Tarsy, D. (2008). Topiramate in essential tremor: findings from doubleblind, placebo-controlled, crossover trials. *Clinical Neuropharmacology, 31*(2), 97–103. doi:10.1097/WNF.0b013e3180d09969

Delay, C., Tremblay, C., Brochu, E., Paris-Robidas, S., Emond, V., Rajput, A. H., . . . Calon, F. (2014). Increased LINGO1 in the cerebellum of essential tremor patients. *Movement Disorders, 29*, 1637-1647. doi:10.1002/mds.25819

Deng, H., Wu, S., & Jankovic, J. (2019). Essential tremor: Genetic update. *Expert Reviews in Molecular Medicine, 21*, e8-e8. doi:10.1017/erm.2019.7

Deuschl, G., Raethjen, J., Hellriegel, H., & Elble, R. (2011). Treatment of patients with essential tremor. *The Lancet Neurology, 10*(2), 148–161. doi:10.1016/S1474-4422(10)70322-7

Deuschl, G., Wenzelburger, R., Loffler, K., Raethjen, J., & Stolze, H. (2000). Essential tremor and cerebellar dysfunction: Clinical and kinematic analysis of intention tremor. *Brain, 123*, 1568–1580. doi:10.1093/brain/123.8.1568

Dietrichson, P., & Espen, E. (1987). Primidone and propranolol in essential tremor: A study based on quantitative tremor recording and plasma anticonvulsant levels. *Acta Neurologica Scandinavica, 75*(5), 332–340. doi:10.1111/j.1600-0404.1987.tb05455.x

Dlugos, C. A. (2008). Ethanol-related increases in degenerating bodies in the Purkinje neuron dendrites of aging rats. *Brain research*, *1221*, 98–107. doi:10.1016/j.brainres.2008.05.015

Dogu, O., Louis, E. D., Sevim, S., Kaleagasi, H., & Aral, M. (2005). Clinical characteristics of essential tremor in Mersin, Turkey - a population-based door-to-door study. *Journal of Neurology, 252*(5), 570–574. doi:10.1007/s00415-005-0700-8

Dogu, O., Louis, E. D., Tamer, L., Una, O., Yilmaz, A., & Kaleagasi, H. (2007). Elevated blood lead concentrations in essential tremor: A case‐control study in Mersin, Turkey. *Environmental Health Perspectives*, *115*, 1564– 1568. doi:10.1289/ehp.10352

Elbelkemy, M., Shalash, A., Mansour, A., Hamed, E., & Abdelalim, H. M. (2020). Non motor symptoms in patients with essential tremor. *Quarterly Journal of Medicine*, *113*(Supplement_1). doi:10.1093/qjmed/hcaa054.003

Ferreira, J. J., Mestre, T. A., Lyons, K. E., Benito-León, J., Tan, E. K., Abbruzzese, G., … Deuschl, G. (2019). MDS commissioned review: MDS evidence-based review of treatments for essential tremor. *Movement Disorders, 34*, 950-958. doi:10.1002/mds.27700

Ferrer, I., Fabregues, I., Pineda, M., Gracia, I., & Ribalta, T. (1984). A Golgi study of cerebellar atrophy in human chronic alcoholism. *Neuropathology and Applied Neurobiology, 10*(4), 245–53. doi:10.1111/j.1365-2990.1984.tb00357.x

Findley, L. J., Cleeves, L., & Calzetti, S. (1985). Primidone in essential tremor of the hands and head: A double blind controlled clinical study. *Journal of Neurology, Neurosurgery, and Psychiatry, 48*, 911–915. doi:10.1136/jnnp.48.9.911

Ghika, A., Kyrozis, A., Potagas, C., & Louis E. D. (2015). Motor and non-motor features: Differences between patients with isolated essential tremor and patients with both essential tremor and Parkinson's disease. *Tremor and Other Hyperkinetic Movements, 5,* 335. doi:10.7916/D83777WK

Giordano, M., Caccavella, V. M., Zaed, I., Manzillo, L. F., Montano, N., Olivi, A., & Polli, F. M. (2020). Comparison between deep brain stimulation and magnetic resonance-guided focused ultrasound in the treatment of essential tremor: A systematic review and pooled analysis of functional outcomes. *Journal of Neurology, Neurosurgery, and Psychiatry.* Advance online publication. doi:10.1136/jnnp-2020-323216

Gironell, A., Ribosa-Nogué, R., Gich, I., Marin-Lahoz, J., & Pascual-Sedano, B. (2015). Severity stages in essential tremor: A long-term retrospective study using the glass scale. *Tremor and other hyperkinetic movements*, *5*, 299. doi:10.7916/D8DV1HQC

Grimaldi, G., & Manto, M. (2013). Is essential tremor a Purkinjopathy? The role of the cerebellar cortex in its pathogenesis. *Movement Disorders, 28*, 1759–1761. doi:10.1002/mds.25645

Guglielmino, G., Moraes, B. T., Villanova, L. C., Padovani, M., & Biase, N. G. (2018).

Comparison of botulinum toxin and propranolol for essential and dystonic vocal tremors. *Clinics*, *73*, e87. doi:10.6061/clinics/2018/e87

Gurey, L. E., Sinclair, C. F., & Blitzer, A. (2013). A new paradigm for the management of essential vocal tremor with botulinum toxin. *The Laryngoscope, 123*, 2497-2501. doi:10.1002/lary.24073

Hallett, M. (2014) Tremor: pathophysiology. *Parkinsonism Related Disorder, 20*(Supplement 1), S118–S122. doi:10.1016/S1353-8020(13)70029-4

Haubenberger, D., & Hallett, M. (2018). Essential tremor. *The New England Journal of Medicine, 378*, 1802-1810. doi:10.1056/NEJMcp1707928

Herrnstadt, G., McKeown, M. J., & Menon, C. (2019). Controlling a motorized orthosis to follow elbow volitional movement: Tests with individuals with pathological tremor. *Journal of Neuroengineering Rehabilitation*, *16,* 23. doi:10.1186/s12984-019-0484-130709409

Herrnstadt, G., & Menon, C. (2016). Voluntary-driven elbow orthosis with speed-controlled tremor suppression. *Frontiers in Bioengineering and Biotechnology*, *4*, 29. doi:10.3389/fbioe.2016.00029

Hertegård, S., Granqvist, S., & Lindestad, P. A. (2000). Botulinum toxin injections for essential voice tremor. *The Annals of Otology, Rhinology, and Laryngology, 109*(2), 204–209. doi:10.1177/000348940010900216

Huang, H., Zhao, Q., Ning, P., Shen, Q., Wang, H., Xie, D., . . . Xu, Y. (2020). Non‐motor symptoms are associated with midline tremor in essential tremor. *Acta Neurologica Scandinavica, 142*(5), 501-510. doi:10.1111/ane.13290

Hubble, J. P., Busenbark, K. L., Pahwa, R., Lyons, K., & Koller, W. C. (1997). Clinical expression of essential tremor: Effects of gender and age. *Movement Disorder, 12,* 969–972. doi:10.1002/mds.870120620

Janicki, S. C., Cosentino, S., & Louis, E. D. (2013). The cognitive side of essential tremor: What are the therapeutic implications? *Therapeutic Advances in Neurological Disorders, 6*(6), 353–368. doi:10.1177/1756285613489591

Jankovic, J., Cardoso, F., Grossman, R. G., & Hamilton, W. J. (1995). Outcome after stereotactic thalamotomy for parkinsonian, essential, and other types of tremor. *Neurosurgery, 37*, 680–687. doi:10.1227/00006123-199510000-00011

Jhunjhunwala, K., & Pal, P. K. (2014). The non-motor features of essential tremor: a primary disease feature or just a secondary phenomenon? *Tremor and Other Hyperkinetic Movements, 4*, 255. doi:10.7916/D8D798MZ

Jimenez-Jimenez, F., Alonso-Navarro, H., Garcia-Martin, E., & Agundez, J. (2020). Sleep disorders in essential tremor: Systematic review and meta-analysis. *Sleep Journal, 43*(9), 1-11. doi:10.1093/sleep/zsaa039

Jimenez‐Jimenez, F. J., de Toledo‐Heras, M., Alonso‐Navarro, H., Ayuso-Peralta, L., Arévalo-Serrano, J., Ballesteros-Barranco, A. … Barcenilla, B. (2007). Environmental risk factors for essential tremor. *European Neurology, 58*, 106– 113. doi:10.1159/000103646

Kang, A., Moon, S., Cho, S., Park, S., Jung, W., Park, J., … Kwon, S. (2020). Herbal medicine treatments for essential tremor: A retrospective chart review study. *Journal of Herbal Medicine, 19*, 100295. doi:10.1016/j.hermed.2019.100295

Kang, N., & Cauraugh, J. H. (2017). Does non-invasive brain stimulation reduce essential tremor? A systematic review and meta-analysis. *PLoS ONE, 12*, e0185462. doi:10.1371/journal.pone.0185462

Kim, M., Jung, N. Y., Park, C. K., Chang, W. S., Jung, H. H., & Chang, J. W. (2017). Comparative evaluation of magnetic resonance-guided focused ultrasound surgery for essential tremor. *Stereotactic and Functional Neurosurgery, 95*(4), 279–286. doi:10.1159/000478866

Koller, W. C., Lyons, K. E., Wilkinson, S. B., Troster, A. I., & Pahwa, R. (2001). Long-term safety and efficacy of unilateral deep brain stimulation of the thalamus in essential tremor. Movement Disorders, 16(3), 464-468. doi:10.1002/mds.1089

Koller, W., Pahwa, R., Busenbark, K., Hubble, J., Wilkinson, S., Lang, A., . . . Olanow, C. W. (1997). High‐frequency unilateral thalamic stimulation in the treatment of essential and parkinsonian tremor. Annals of Neurology, 42(3), 292-299. doi:10.1002/ana.410420304

Kuo, S., Wang, J., Tate, W. J., Pan, M., Kelly, G. C., Gutierrez, J., . . . Faust, P. L. (2017). Cerebellar pathology in early onset and late onset essential tremor. *The Cerebellum, 16*(2), 473-482. doi:10.1007/s12311-016-0826-5

Lacritz, L., H., Dewey, R., Giller, C., & Cullum, C.M. (2002). Cognitive functioning in individuals with ‘‘benign’’ essential tremor. *Journal of the International Neuropsychological Society, 8*, 125–129, doi:10.1017/S1355617702001121

Lin, C., Louis, E., Faust, P., Koeppen, A., Vonsattel, J., & Kuo, S. (2014). Abnormal climbing fibre-Purkinje cell synaptic connections in the essential tremor cerebellum. *Brain, 137*, 3149-3159. doi:10.1093/brain/awu281

Lorenz, D., Poremba, C., Papengut, F., Schreiber, S., & Deuschl, G. (2011). The psychosocial burden of essential tremor in an outpatient- and a community-based cohort. *European Journal of Neurology, 18*, 972–979. doi:10.1111/j.1468-1331.2010.03295.x

Louis, E. D., Agnew, A., Gillman, A., Gerbin, M., & Viner, A.S. (2011). Estimating annual rate of decline: prospective, longitudinal data on arm tremor severity in two groups of essential tremor cases. *Journal of Neurology, Neurosurgery, and Psychiatry, 82*(7), 761–765. doi:10.1136/jnnp.2010.229740.

Louis, E. D., Barnes, L., Albert, S. M., Cote, L., Schneier, F. R., Pullman, S. L., & Yu, Q. (2001). Correlates of functional disability in essential tremor. *Movement Disorders, 16*, 914-920. doi:10.1002/mds.1184

Louis, E. D., Benito‐Leon, J., & Bermejo‐Pareja, F. (2009). Population‐based study of baseline ethanol consumption and risk of incident essential tremor. *Journal of Neurology, Neurosurgery, and Psychiatry, 80,* 494– 497. doi:10.1136/jnnp.2008.162701

Louis, E. D. (2016). Essential tremor: A common disorder of Purkinje Neurons? *Neuroscientist, 22*(2), 108-118. doi:10.1177/1073858415590351

Louis, E. D. (2009). Essential tremors: A family of neurodegenerative disorders?. *Archives of neurology*, *66*, 1202–1208. doi:10.1001/archneurol.2009.217

Louis, E. D. (2010). Essential tremor: Evolving clinicopathological concepts in an era of intensive post-mortem inquiry. *The Lancet Neurology, 9*, 613-622. doi:10.1016/S1474-4422(10)70090-9

Louis, E. D. (2013). ‘Essential tremor’ or ‘the essential tremors’: Is this one disease or a family of diseases? *Neuroepidemiology, 42*, 81–89. doi:10.1159/000356351

Louis, E. D. (2005). Essential tremor. *The Lancet Neurology, 4*(2), 100–110. doi: 10.1016/S1474-4422(05)00991-9

Louis, E. D. (2014). From neurons to neuron neighborhoods: The rewiring of the cerebellar cortex in essential tremor. *The Cerebellum, 13*(4), 501-512. doi:10.1007/s12311-013-0545-0

Louis, E. D. (2016). Non-motor symptoms in essential tremor: A review of the current data and state of the field. *Parkinsonism & related disorders*, *22,* S115–S118. doi:10.1016/j.parkreldis.2015.08.034

Louis, E. D., Factor-Litvak, P., Parides, M., Andrews, L., Santella, R. M., & Wolff, M. S. (2006). Organochlorine pesticide exposure in essential tremor: A case‐control study using biological and occupational exposure assessments. *Neurotoxicology 27*(4), 579–586. doi:10.1016/j.neuro.2006.03.005

Louis, E. D., & Faust, P. L. (2020). Essential tremor pathology: Neurodegeneration and reorganization of neuronal connections. *Nature Reviews. Neurology, 16*(2), 69. doi:10.1038/s41582-019-0302-1

Louis, E. D., Faust, P. L., Vonsattel, J. P., Honig, L. S., Henchcliffe, C., Pahwa, R., . . . Lawton, A. (2017). Older onset essential tremor: More rapid progression and more degenerative pathology. *Movement Disorders, 24*, 1606-1612. doi:10.7916/d8862n6w

Louis, E. D., Ford, B., Frucht, S., Barnes, L. F., X-Tang, M., & Ottman, R. (2001). Risk of tremor and impairment from tremor in relatives of patients with essential tremor: A community-based family study. *Annals of Neurology, 49*, 761-769. doi:10.1002/ana.1022

Louis, E. D., Ford, B., & Frucht, S. (2003). Factors associated with increased risk of head tremor

in essential tremor: A community-based study in northern Manhattan. *Movement Disorder, 18*(4): 432–436. doi:10.1002/mds.10395

Louis, E. D., Hernandez, N., Ionita-Laza, I., Ottman, R., & Clark, L. N. (2012). Does rate of progression run in essential tremor families? Slower vs. faster progressors. *Parkinsonism & Related Disorders, 19*(3), 363-366. doi:10.1016/j.parkreldis.2012.10.005

Louis, E.D., Huey, E.D., Gerbin, M., & Viner, A.S. (2012). Apathy in essential tremor, dystonia, and Parkinson's disease: A comparison with normal controls. *Movement Disorders, 27*(3):432–434. doi:10.1002/mds.24049

Louis, E. D., Lee, M., Babij, R., Ma, K., Cortés, E., Vonsattel, J. P., & Faust, P. L. (2014). Reduced Purkinje cell dendritic arborization and loss of dendritic spines in essential tremor. *Brain*, *137*, 3142–3148. doi:10.1093/brain/awu31

Louis, E. D., Jiang, W., Pellegrino, K. M., Rios, E., Factor-Litvak, P., Henchcliffe, C., & Zheng, W. (2008). Elevated blood harmane (1-methyl-9H-pyrido[3,4-b]indole) concentrations in essential tremor. *Neurotoxicology, 29*(2):294-300. doi:10.1016/j.neuro.2007.12.001

Louis, E. D., Jurewicz, E. C., Applegate, L., Factor-Litvak, P., Parides, M., Andrews, L., … Todd, A. (2003). Association between essential tremor and blood lead concentration. *Environmental health perspectives*, *111*, 1707–1711. doi:10.1289/ehp.6404

Louis, E. D., Jurewicz, E. C., Applegate, L., Luchsinger, J. A., Factor-Litvak, P., & Parides, M. (2004). Semiquantitative study of current coffee, caffeine, and ethanol intake in essential tremor cases and controls. *Movement Disorders, 19*(5):499-504. doi:10.1002/mds.20035

Louis, E. D., Jurewicz, E. C., & Parides, M. K. (2007). Case‐control study of nutritional antioxidant intake in essential tremor. *Neuroepidemiology*, *24*(4), 203– 208. doi:10.1159/000084713

Louis, E. D., Kuo, S. H., Wang, J., Tate, W. J., Pan, M. K., Kelly, G. C., ... Faust, P. L. (2017). Cerebellar pathology in familial vs. sporadic essential tremor. *Cerebellum (London, England)*, *16*(4), 786–791. doi:10.1007/s12311-017-0853-x

Louis, E. D., Ma, K., Babij, R., Cortés, E., Liem, R. K., Vonsattel, J. G., & Faust, P. L. (2012). Neurofilament protein levels: Quantitative analysis in essential tremor cerebellar cortex. *Neuroscience Letters, 518*, 49-54. doi:10.1016/j.neulet.2012.04.054

Louis, E. D., & Michalec, M. (2014). Semi-quantitative data on ethanol consumption in 354 ET cases and 370 controls. *Journal of the neurological sciences*, *347*(1-2), 174–178. doi:10.1016/j.jns.2014.09.042

Louis, E. D., Rios, E., Pellegrino, K. M., Jiang, W., Factor-Litvak, P., & Zheng, W. (2008). Higher blood harmane (1-methyl-9H-pyrido[3,4-b]indole) concentrations correlate with lower olfactory scores in essential tremor. *Neurotoxicology*, *29*(3), 460–465. doi:10.1016/j.neuro.2008.02.013

Louis, E. D., Zheng, W., Applegate, L., Shi, L., & Factor-Litvak, P. (2005). Blood harmane concentrations and dietary protein consumption in essential tremor. *Neurology*, *65*(3), 391–396. doi:10.1212/01.wnl.0000172352.88359.2d

Louis, E. D., & Zheng, W. (2010). Beta-carboline alkaloids and essential tremor: exploring the environmental determinants of one of the most prevalent neurological diseases. *TheScientificWorldJournal*, *10*, 1783–1794. doi:10.1100/tsw.2010.159

Louis, E. D., Zheng, W., Jurewicz, E. C., Watner, D., Chen, J., Factor-Litvak, P., & Parides, M. (2002). Elevation of blood beta-carboline alkaloids in essential tremor. *Neurology*, *59*, 1940–1944. doi:10.1212/01.wnl.0000038385.60538.19

Loureiro, R. C. V., Belda-Lois, J. M., Lima, E. R., Pons, J. L., Sanchez-Lacuesta, J. J., & Harwin, W. S. (2005). Upper Limb tremor suppression in ADL via an orthosis incorporating a controllable double viscous beam actuator. *Proceedings of the 2005 IEEE 9th International Conference on Rehabilitation Robotics*, 2005, 119–122. doi:10.1109/ICORR.2005.1501065

Mally, J., & Baranyi, M. (1994). Change in the concentrations of amino acids in cisternal CSF of patients with essential tremor. *Journal of Neurology, Neurosurgery, and Psychiatry, 57*, 1012-1013

Mally, J., Baranyi, M., & Vizi, E. S. (1996). Change in the concentrations of amino acids in CSF and serum of patients with essential tremor. *Journal of Neural Transmission, 103*(5), 555–560. doi:10.1007/BF01273153

Maneski, P. L., Jorgovanovic, N., Ilic, V., Dosen, S., Keller, T., Popovic, M. B., & Popovic, D. B. (2011). Electrical stimulation for the suppression of pathological tremor. *Medical and Biological Engineering and Computing,49,* 1187–1193. doi:10.1007/s11517-011-0803-621755318

Mavroudis, I., Petridis, F., & Kazis, D. (2019). Neuroimaging and neuropathological findings in essential tremor. *Acta Neurologica Scandinavica, 139*(6), 491-496. doi:10.1111/ane.13101

Murray T. J. (1976). Long-term therapy of essential tremor with propranolol. *Canadian Medical*

Association journal, *115*, 892–894. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1879108/

Musacchio, T., Purrer, V., Papagianni, A., Fleischer, A., Mackenrodt, D., Malsch, C., ... Klebe, S. (2016). Non-motor symptoms of essential tremor are independent of tremor severity and have an impact on quality of life. *Tremor and Other Hyperkinetic Movements*, *6*, 361. doi:10.7916/D8542NCH

Nazzaro, J. M., Lyons, K. E., & Pahwa, R. Deep brain stimulation for essential tremor. *Handbook of Clinical Neurology, 116*, 155–166. doi:10.1016/B978-0-444-53497-2.00013-9

Nestrasil, I., Svatkova, A., Rudser, K. D., Chityala, R., Wakumoto, A., Mueller, B. A., … Bushara, K. (2018). White matter measures correlate with essential tremor severity-A pilot diffusion tensor imaging study. *Brain and behavior*, *8*(8), e01039. doi:10.1002/brb3.1039

Nicoletti, A., Mostile, G., Cappellani, R., Contrafatto, D., Arabia, G., Lamberti, P., … Zappia, M. (2011). Wine drinking and essential tremor: A possible protective role. *Movement Disorders, 26*, 1310– 1315. doi:10.1002/mds.23603

Ondo, W. G., Jankovic, J., Connor, G. S., Pahwa, R., Elble, R., Stacy, M. A., … Hulihan, J. F. (2006). Topiramate in essential tremor. *Neurology, 66*, 672–677. doi:10.1212/01.wnl.0000200779.03748.0f

Ong, Y. L., Deng, X., & Tan, E. K. (2019). Etiologic links between environmental and lifestyle factors and Essential tremor. *Annals of clinical and translational neurology*, *6*, 979–989. doi:10.1002/acn3.758

Pahwa, R., Busenbark, K., Swanson-Hyland, E. F., Dubinsky, R. M., Hubble, J. P., Gray, C., & Koller, W. C. (1995). Botulinum toxin treatment of essential head tremor. *Neurology, 45*, 822–824. doi:10.1212/wnl.45.4.822

Pahwa, R., Lyons, K. E., Wilkinson, S. B., Simpson, J., Richard K, Ondo, W. G., Tarsy, D., . . . Jankovic, J. (2006). Long-term evaluation of deep brain stimulation of the thalamus. Journal of Neurosurgery, 104(4), 506. doi:10.3171/jns.2006.104.4.506

Pahwa, R., Lyons, K. E., Wilkinson, S. B., Tröster, A. I., Overman, J., Kieltyka, J., & Koller, W. C. (2001). Comparison of thalamotomy to deep brain stimulation of the thalamus in essential tremor. Movement Disorders, 16(1), 140-143. doi:10.1002/1531-8257(200101)16:1<140::AID-MDS1025>3.0.CO;2-T

Paparella, G., Ferrazzano, G., Cannavacciuolo, A., Cogliati Dezza, F., Fabbrini, G., Bologna, M., & Berardelli, A. (2018). Differential effects of propranolol on head and upper limb tremor in patients with essential tremor and dystonia. *Journal of Neurology, 265*, 2695–2703. doi:10.1007/s00415-018-9052-z

Paris-Robidas, S., Brochu, E., Sintes, M., Emond, V., Bousquet, M., Vandal, M., . . . Calon, F. (2012). Defective dentate nucleus GABA receptors in essential tremor. *Brain, 135*, 105-116. doi:10.1093/brain/awr301

Park, Y. S., Jung, N. Y., Na, Y. C., & Chang, J. W. (2019). Four-year follow-up results of magnetic resonance-guided focused ultrasound thalamotomy for essential tremor. *Movement Disorders, 34*(5), 727–734. doi:10.1002/mds.27637

Peng, J., Wang, L., Li, N., Li, J., Duan, L., & Peng, R. (2020). Distinct non‐motor features of

essential tremor with head tremor patients. *Acta Neurologica Scandinavica, 142*, 74-82. doi:10.1111/ane.13242

Picciotto, M. R., & Zoli, M. (2008). Neuroprotection via nAChRs: The role of nAChRs in neurodegenerative disorders such as Alzheimer's and Parkinson's disease. *Frontiers in Bioscience, 13*, 492– 504. doi:10.2741/2695

Pietracupa, S., Bologna, M., Bharti, K., Pasqua. G., Tommasin, S., Elifani, F., … Pantano, P. (2019). White matter rather than gray matter damage characterizes essential tremor. *European Radiology, 29*, 6634–6642. doi:10.1007/s00330-019-06267-9

Prakash, K. M., Fook‐Choong, S., Yuen, Y., Tan, E. K. (2006). Exploring the relationship between caffeine intake and essential tremor. *Journal of the Neurological Sciences, 251*, 98– 101. doi:10.1016/j.jns.2006.09.007

Prasad, S., Pandey, U., Saini, J., Ingalhalikar, M., & Pal, P. K. (2019). Atrophy of cerebellar peduncles in essential tremor: A machine learning–based volumetric analysis. *European Radiology, 29*, 7037–7046. doi:10.1007/s00330-019-06269-7

Putzke, J. D., Whaley, N. R., Baba, Y., Wszolek, Z. K., & Uitti, R. J. (2006). Essential tremor: Predictors of disease progression in a clinical cohort. *Journal of Neurology, Neurosurgery and Psychiatry, 77*, 1235-1237. doi:10.1136/jnnp.2006.086579

Quik, M., Perez, X. A., & Bordia, T. (2012). Nicotine as a potential neuroprotective agent for Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society*, *27*, 947–957. doi:10.1002/mds.25028

Rajput, A. H., Robinson, C. A., Rajput, M L., Robinson, S. L., & Rajput, A. (2012). Essential tremor is not dependent on cerebellar Purkinje cell loss. *Parkinsonism & Related*

Disorders 18, 626-628. doi:10.1016/j.parkreldis.2012.01.013

Rajput, A. H., Rozdilsky, B., Ang, L., & Rajput, A. (1993). Significance of Parkinsonian manifestations in essential tremor. *Canandian Journal of Neurological Sciences, 20*(2), 114–17. doi:10.1017/s031716710004765x

Ramon y Cajal, S. (1928). Degeneration and regeneration of the nervous system. Oxford, England: Oxford University Press.

Rocon, E., Belda-Lois, J. M., Ruiz, A. F., Manto, M., Moreno, J. C., & Pons, J. L. (2007). Design and validation of a rehabilitation robotic exoskeleton for tremor assessment and suppression. *IEEE Transactions on Neural Systems and Rehabilitation Engineering, 15,* 367–378. doi:10.1109/TNSRE.2007.90391717894269

Sandoe, C., Krishna, V., Basha, D., Sammartino, F., Tatsch, J., Picillo, M. … Fasano, A. (2018). Predictors of deep brain stimulation outcome in tremor patients. *Brain Stimulation, 11*(3) 592–599. doi:10.1016/j.brs.2017.12.014

Santangelo, G., Trojano, L., Barone, P., Errico, D., Grossi, D., & Vitale, C. (2013). Apathy in Parkinson's disease: Diagnosis, neuropsychological correlates, pathophysiology and treatment. *Behavioural Neurology, 27*(4), 501-513. doi:10.1155/2013/851890

Sasso, E., Perucca, E., Fava, R., & Calzetti, S. (1990). Primidone in the long-term treatment of essential tremor: A prospective study with computerized quantitative analysis. *Clinical Neuropharmacology, 13*, 67–76. doi:10.1097/00002826-199002000-00007

Scarmeas, N., & Louis, E. D. (2007). Mediterranean diet and essential tremor. A case‐control study. *Neuroepidemiology*, *29*(3-4), 170– 177. doi:10.1159/000111579

Schaefer, S. M., Vives Rodriguez, A., & Louis, E. D. (2018). Brain circuits and neurochemical

systems in essential tremor: Insights into current and future pharmacotherapeutic approaches. *Expert Review of Neurotherapeutics, 18*(2), 101-110. doi:10.1080/14737175.2018.1413353

Schneier. F. R., Barnes, L. F., Albert, S. M., & Louis, E. D. (2001). Characteristics of social phobia among persons with essential tremor. *Journal of Clinical Psychiatry, 62*(5), 367–372. doi:10.4088/jcp.v62n0511

Sengul, Y. (2020). Auditory and olfactory deficits in essential tremor - Review of the current evidence. *Tremor and Other Hyperkinetic Movements, 10*(3), 1-15. doi:10.5334/tohm.57

Sengul, Y., Sengul, H. S., Gokcal, E., Ustun, I., Ozturk, A., Yilmaz, O., . . . Louis, E.D. (2020). Alexithymia is a non motor symptom of essential tremor regardless of the presence of depression and anxiety. *Neurological Research, 42*, 946-951. doi:10.1080/01616412.2020.1792702

Sengul, Y., Sengul, H. S., Yucekaya, S. K., Yucel, S., Bakim, B., Pazarci, N. K., & Özdemir, G. (2014). Cognitive functions, fatigue, depression, anxiety, and sleep disturbances: Assessment of nonmotor features in young patients with essential tremor. *Acta Neurologica Belgica, 115*(3), 281-287. doi:10.1007/s13760-014-0396-6

Sharma, S., & Pandey, S. (2020). Treatment of essential tremor: Current status. *Postgraduate Medical Journal, 96*(1132), 84-93. doi:10.1136/postgradmedj-2019-136647

Shimohama, S. (2009). Nicotinic receptor‐mediated neuroprotection in neurodegenerative disease models. *Biological and Pharmaceutical Bulletin, 32*, 332– 336. doi:10.1248/bpb.32.332

Sinai, A., Nassar, M., Eran, A., Constantinescu, M., Zaaroor, M., Sprecher, E., & Schlesinger, I.

(2019). Magnetic resonance-guided focused ultrasound thalamotomy for essential tremor: A 5-year single-center experience. *Journal of Neurosurgery*. Advance online publication. doi:10.3171/2019.3.JNS19466

Singer, C., Sanchez-Ramos, J., & Weiner, W. J. (1994). Gait abnormality in essential tremor. *Movement Disorder, 9*(2), 193–196. doi:10.1002/mds.870090212

Soto, M. C. S., & Fasano, A. (2020). Essential tremor: New advances. *Clinical Parkinsonism and related disorders, 3*, 100031. doi:10.1016/j.prdoa.2019.100031

Stefansson, H., Steinberg, S., Petursson, H., Gustafsson, O., Gudjonsdottir, I. H., Jonsdottir, G. A., … Stefansson, K. (2009). Variant in the sequence of the LINGO1 gene confers risk of essential tremor. *Nature Genetics, 41*(3), 277–279. doi:10.1038/ng.299

Sullivan, K., Hauser, R., & Zesiewicz, T. (2004). Essential tremor - epidemiology, diagnosis, and treatment. *The Neurologist, 10*(5), 250-258. doi:10.1097/01.nrl.0000138736.07840.b2

Tasker, R. R., Munz, M., Junn, F. S., Kiss, Z. H., Davis, K., Dostrovsky, J. O., & Lozano, A. M. (1997). Deep brain stimulation and thalamotomy for tremor compared. *Acta Neurochirurgica Supplement, 68*, 49–53. doi:10.1007/978-3-7091-6513-3_9

Wang, T. R., Dallapiazza, R. F., Moosa, S., Huss, D., Shah, B. B., & Elias, W. J. (2018). Thalamic deep brain stimulation salvages failed focused ultrasound Thalamotomy for essential tremor: A case report. *Stereotactic and Functional Neurosurgery, 96*, 60–64. doi:10.1159/000486646

Warrick, P., Dromey, C., Irish, J. C., Durkin, L., Pakiam, A., & Lang, A. (2000). Botulinum

toxin for essential tremor of the voice with multiple anatomical sites of tremor: a crossover design study of unilateral versus bilateral injection. *The Laryngoscope, 110*, 1366–1374. doi:10.1097/00005537-200008000-00028

Winkler, G. F., & Young, R. R. (1974). Efficacy of chronic propranolol therapy in action tremors of the familial, senile or essential varieties. *The New England Journal of Medicine, 290*, 984–988. doi:10.1056/NEJM197405022901802

Wissel, J., Masuhr, F., Schelosky, L., Ebersbach, G., & Poewe, W. (1997). Quantitative assessment of botulinum toxin treatment in 43 patients with head tremor. *Movement Disorders, 12*, 722–726. doi:10.1002/mds.870120516

Witjaz, T., Carron, R., Krack, P., Eusebio, A., Vaugoyeau, M., Hariz, M., … Regis, J. (2015). A prospective single-blind study of gamma knife thalamotomy for tremor. *Neurology, 85*, 1562–1568. doi:10.1212/WNL.0000000000002087

Yao, Y., Wang, Y., & Yang, X. (2015). Related factors and prevalence for the essential tremor disease of Uygur residents in Hetian, Xinjiang UygurAutonomous Region. *Zhonghua Yi Xue Za Zhi*, *95*, 69–72. Retrieved from https://pubmed.ncbi.nlm.nih.gov/25876815/

Yokota, O., Tsuchiya, K., Terada, S., Oshima, K., Ishizu, H., Matsushita, M., … Akiyama, H. (2007). Alcoholic cerebellar degeneration: A clinicopathological study of six Japanese autopsy cases and proposed potential progression pattern in the cerebellar lesion. *Neuropathology, 27*(2), 99– 113. doi:10.1111/j.1440-1789.2006.00748.x

Zesiewicz, T. A., Elble, R. J., Louis, E. D., Gronseth, G. S., Ondo, W. G., Dewey, R. B., ...

Weiner, W. J. (2011). Evidence-based guideline update: Treatment of essential tremor: Report of the Quality Standards subcommittee of the American Academy of Neurology. *Neurology*, *77*, 1752–1755. doi:10.1212/WNL.0b013e318236f0fd

Zirh, A., Reich, S. G., Dougherty, P. M., & Lenz, F. A. (1999). Stereotactic thalamotomy in the treatment of essential tremor of the upper extremity: Reassessment including a blinded measure of outcome. *Journal of Neurology, Neurosurgery, and Psychiatry, 66*, 772–775. doi:10.1136/jnnp.66.6.772