Essential Tremor Reaserch Program: Cannabidiol Anti-Tremor Action and Mechanisms

Adrian Handforth, MD

Summary:

People tend to think of "medical marijuana" as a unitary substance that may have beneficial medical effects but also necessarily causes mood- and mind-altering effects. Actually marijuana has many related chemicals, called cannabinoids. The one known as "THC" (tetrahydrocannabinol) causes mood alteration and effects on the mind, and can have serious side effects such as uncontrolled behavior, hallucinations, and addiction. However there ia another cannabinoid known as "CBD" (cannabidiol). Years of research on humans and animals have indicated that, unlike THC, CBD does not cause undesirable mind- and mood-altering effects, yet preliminary evidence has shown benefit for epilepsy, pain, anxiety and other disorders.

In our interactions with persons with essential tremor (ET) we have encountered many over the years who reported that marijuana was quite effective in suppressing tremor. We have also confirmed with personal observation worsening of tremor in a patient without marijuana compared to when he was using it. More recently we observed a patient who had virtual elimination of tremor after taking CBD. This observation, in addition to the general finding that CBD appears to confer most or all the benefits of "medical marijuana", lead us to believe that CBD, or a derivative of it, has potential as ET therapy.

Research has shown that CBD can cause effects through several mechanisms in the brain. In this project we seek to establish whether CBD suppresses tremor in a rodent model and then study which mechanism is responsible for the anti-tremor action.

The harmaline mouse model of eseential tremor will be utilized. In the model, the drug harmaline is given to cause tremor that lasts 2 hours. An initial experiment will determine the relationship between cannabidiol dose and degree of tremor suppression. Next, a series of experiments will be performed using selective receptor antagonists and agonists to determine whether cannabidiol is suppressing tremor by activating specific receptors.

CBD does not activate the brain's cannabinoid (CB1 and CB2) receptors directly, thus avoiding the undesired effects of THC, which does. Howeverr CBD can still indirectly activate these receptors by raising the level of a brain chemical (endogenous cannabinoid) that acts on these receptors in a natural way. Some evidence indicates that CBD suppresses pain this way. To see whether CBD suppresses tremor through such a mechanism, we will give mice specific CB1 or CB2 blockers at the same time as we give CBD and see whether they prevent CBD from suppressing tremor.

In animal models CBD has been found to have antidepressant and anti-anxiety effects by activating a serotonin receptor subtype (5HT1a) and an unusual receptor called TRPV1. To find out whether these receptors might mediate tremor suppression by CBD we wil co-administer specific 5HT1a or TRPV1 receptor blockers along with CBD and see whether they stop CBD from suppressing tremor.

A very interesting recent discovery is the finding that CBD alters the shape of part of the brain's glycine receptors so that they become more sensitive to glycine that is naturally released by brain cells. This property, called positive allosteric modulation, has been shown responsible for reducing pain sensitivity and alleviating symptoms in a model of excessive startle disorder. We will co-administer a drug that specifically blocks the attachment of CBD to the glycine receptor (DD-CBD) and see whether it prevents CBD from suppressing harmaline tremor. We will also give a derivative of CBD that specifically acts as a positive modulator of glycine receptors, DH-CBD, and see whether it suppresses tremor.

The significance of the proposed work is two-fold. The first is that a finding that CBD suppresses tremor in an animal model of essential tremor may provide justification for a clinical trial of CBD for ET. More importantly, the determination of the anti-tremor mechanism of CBD would enable the modification of CBD so as to design a medication that is more potent and selective, and thus well tolerated and effective, for ET.

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1. Specifc Aims

We have encountered many ET patients who report substantial anti-tremor benefit on using marijuana. More recently we saw marked tremor reduction with cannabidiol (CBD) use in a 54 year man with tremor since childhood. Although once considered inert due to low affinity to cannabinoid receptors CB1 and CB2, it is now appreciated that CBD exerts medical benefits in the absence of the psychotropic actions seen with THC.

CBD exerts CNS effects both directly on several neurotransmitter receptors, and also indirectly by raising the level of the endogenous cannabinoid anandamide (AEA). CBD has direct agonist actions on the 5HT1a and TRPV1 receptors and is a positive allosteric modulator of the glycine receptor. Although CBD has poor affinity for CB1 and CB2 receptors, it affects the transport of endogenous cannabinoids and inhibits fatty acid amide hydrolase, leading to elevation of AEA that then activates CB1, CB2, and TRPV1 receptors. By acting via AEA, CBD may thus indirectly activate these 3 receptors in a way that is physiological, avoiding the psychoactive effects associated with direct cannabinoid receptor activation.

Aim 1: Determine the effect of CBD on harmaline tremor.

The purpose of this experiment is to verify that CBD suppresses tremor in the harmaline mouse model, and to identify the dosages that suppress tremor by 50% and by 80%. This Aim will provide necessary information for the Aims below.

Aim 2: Deteremine whether CBD suppresses tremor by activating the CB1 receptor

CBD may activate CB1 receptors indirectly by elevating AEA. Several actions of CBD that have been reported to be CB1 receptor-dependent include reduction of pain, seixures and compulsive activity in rodent models. To address this potential mechanism we will assess whether the CB1 antagonist AM251 blocks the anti-tremor action of CBD, and whether the CB1 receptor agonist ACEA suppresses harmline tremor.

Aim 3: Determine whether CBD suppresses tremor by activating the CB2 receptor

CBD also could activate CB2 receptors indirectly by elevating AEA. CB2 receptor-dependent effects of CBD have not been described, but CB2 receptors are implicated in addiction and other behaviors. To evaluate whether CBD suppresses tremor by indirectly activating CB2 receptors. we will assess whether the CB2 antagonist AM630 blocks the anti-tremor action of CBD, and whether the CB2 receptor agonist JWH133 suppresses harmaline tremor.

Aim 4: Determine whether CBD suppresses tremor by activating the 5HT1a receptor

CBD exerts antidepressant and anti-nausea effects by activating 5HT1a receptors. We will determine whether the anti-tremor action of CBD is blocked by WAY100635, a potent 5HT1a receptor antagonist.

Aim 5: Determine whether CBD suppresses tremor by activating the TRPV1 receptor

CBD is known to activate TRPV1 receptors both directly and indirectly via AEA elevation. CBD exerts analgesic and anxiolytic effects via the TRPV1 receptor in rodent models. In this Aim we will assess whether the TRPV1 receptor antagonist capsazepine blcoks the anti-tremor action of CBD on harmaline tremor.

Aim 6: Determine whether CBD suppresses tremor via glycine receptors

CBD is a positive allosteric modulator of alpha1- and alpha3-containing glycine receptors, meaning that they bind to part of the alpha subunit other than the glycine binding site, and alter the conformation so that the effect of endogenous glycine is more potent. This mechanism is responsible for some analgesic effects of CBD. Alpha1 is present in brain glycine receptors, including those in the cerebellum.

Using the harmaline model, we will assess whether a derivative that is highly specific for the glycine receptor allosteric site, dehydroxyl-CBD (DH-CBD), suppresses tremor. Next we will assess whether the anti-tremor action of CBD and, if present, of DH-CBD is blocked by an antagonist of the glycine receptor allosteric binding site, didesoxy-CBD (DD-CBD). If an anti-tremor effect of CBD and DH-CBD is blocked by DD-CBD, this will suggest CBD suppresses tremor by modulating brain glycine receptors.

2. Rationale and Relevance to Essential Tremor

Extracts of *Cannabis sativa* contain as many as 60 cannabinoids, and these vary according to affinity to a variety of receptors. The two of main interest are delta 9-tetrahydrocannabinol (THC), and cannabidiol (CBD). THC has psychoactive effects, which can include paranoia, anxiety, delusions, hallucinations and psychosis. Evidence suggests that many of these psychoactive effects arise from direct agonist action on cannabinoid receptors CB1 and CB2, particularly the former. CBD, by contrast, is non-psychoactive, has low affinity for these receptors, and in animal models blocks psychoactive effects of THC. Although once considered inert in view of its relative lack of direct activation of cannabinoid receptors, it has become appreciated that CBD exerts anxiolytic, anti-depressant, anti-psychotic, anti-nociceptive, and anti-seizure effects.

There has been a recent resurgence of interest in CBD. Two pharmaceuticals are investigating its use in several conditions. Thus clinical trials with CBD will be proceeding in future years as with any other investigational medication. Currently a trial of CBD for children with severe epilepsy has enrolled several hundred subjects.

Over 10 years ago we encountered a woman who used marijuana in the evening in order to suppress her tremor the next day so that she could function at work. Since then we have encountered a number of veterans who reported that it was as effective or more effective for tremor than anti-tremor medications. In one patient we observed tremor after he stopped marijuana and after he resumed it; there was a marked difference.

A recent case was instructive. A 54 year old man with ET since childhood had marked head tremor that caused neck pain, and hand tremor so severe that others had to help him drink from a glass. His tremor became partly controlled with a combination of propranolol, primidone and zonisamide. On ingesting CBD for a month he found it possible to stop primidone and zonisamide and remained virtually tremor-free. On stopping CBD for financial reasons, the painful head tremor and marked hand tremor returned.

These observations lead us to consider that CBD may have important potential for the treatment of ET, given the inadequacy of current treatments. CBD binds to a number of receptors and thus may act on tremor by one of several alternative mechanisms. Below we summarize evidence that CBD may exert CNS effects through as many as 5 different neurotransmitter receptors.

Although CBD has poor affinity for CB1 and CB2 receptors, it affects the transport of endogenous cannabinoids and inhibits fatty acid amide hydrolase, leading to elevation of the endogenous cannabinoid anandamide (AEA). AEA then activates CB1 and CB2 receptors, and the vanilloid TRPV1 receptor. By acting via AEA, CBD may thus indirectly activate these 3 receptors in a way that is physiological, avoiding psychoactive effects associated with direct receptor activation. In a tail flick model of pain, CBD exerts analgesic effects via the CB1 receptor, as shown by blockade of the analgesic effect with CB1 antagonists (Malone et al., 2011). CBD reduces marble-burying in mice, a model of obsessive compulsive disorder, an effect blocked by the CB1 antagonist AM251 (Casarotto et al., 2010). The CB1 receptor agonist arachidonyl-2-chloroethylamide (ACEA) raises seizure threshold in rodents, an effect blocked by AM251 (Shafaroodi et al., 2013). The role of CB2 receptors in behavior has not been well studied. Antagonists of the CB2 receptor block nicotine withdrawal symptoms in rodents (Navarette et al., 2013).

CBD activates the 5HT1a receptor. In the learned helplessness model of depression, CBD, 30 mg/kg, is as effective as imipramine. The effect of CBD is blocked by WAY100635, a specific 5HT1a receptor antagonist (Zanelati et al. 2010).

TRPV1 receptors are found in the cerebellum and cerebral cortex. CBD indirectly activates TRPV1 receptors via AEA, and also has moderate direct agonist action. Capsazepine , a TRPV1 receptor antagonist , blocks the analgesic effect of CBD in a rodent model of pain (Costa et al., 2004; Comelli et al., 2008). The TRPV1 receptor medicates CBD anxiolytic effects (Campos et al., 2009).

CBD and some other cannabinoids are positive allosteric modulators of alpha1- (in brain) and alpha3- (in spinal cord) containing glycine receptors, meaning that they bind to part of the alpha subunit and alter the conformation so that the effect of endogenous glycine is more potent. CBD suppresses pain in a rodent model, unless the mice are null for the alpha3 subunit, which is necessary for glycine receptors in the spinal cord that modulate pain (Xiong et al. 2012). Hyperekplexia, or startle disease, is caused by mutations of the brain glycine receptor. The CBD derivative, dehydroxyl-CBD (DH-CBD), is a more selective positive modulator that binds allosterically to the site on the alpha1 and alpha3 subunit that CBD binds to. DH-CBD has potent analgesic activity and alleviates symptoms of hyperekplexia in the mouse model (Xiong et al., 2014). A competitive inhibitor for this binding site is didesoxy-CBD (DD-CBD), which has no analgesic effect, but blocks the analgesic effect of DH-CBD when co-administered.

Similarly, these compounds may be useful in assessing whether CBD (or DH-CBD) suppresses tremor via the glycine receptor. (An antagonist of the glycine receptor cannot be used to test for this mechanism of CBD action, such as strychnine, as it would cause violent convulsions.)

Figure 1 shows that CBD, 60 mg/kg, given intraperitoneally, reduces harmaline-induced tremor significantly compared to mice given vehicle. This dose is lower than some doses described in the literature in other behavioral studies, in which 100 mg/kg has been administered.

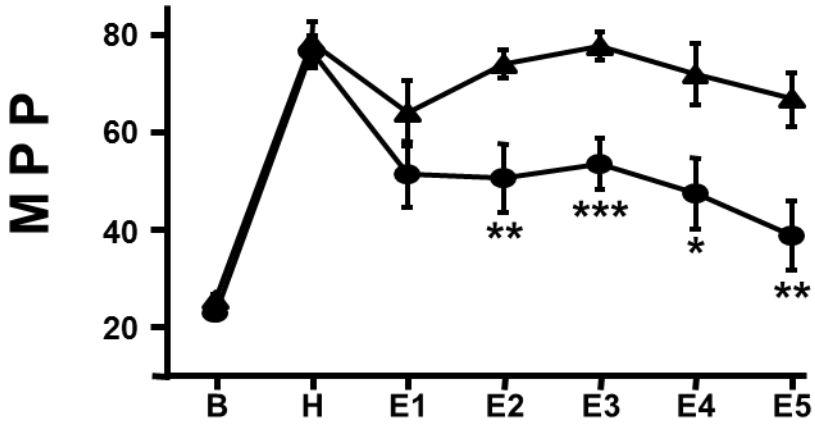

Fig. 1. The effect of cannabidiol on harmaline-induced tremor in C57BL6 mice. Data points show the percentage of 1-32 Hz motion power that falls within the 10-16 Hz tremor bandwidth (Motion Power Percentage, MPP). After a 15-minute baseline epoch (B) and a 15-minute epoch after administration of harmaline (H), 20 mg/kg, intraperitoneal cannabidiol, 60 mg/kg, or vehicle (alcohol:cremophor:saline::1:4:75; 4 mll/kg) were administered, and motion power measured for 5 additional 15-minute epochs (E1 to E5). In control mice (n = 9, triangles), the proportion of motion power in the 10-16 Hz bandwidth increases markedly from baseline after harmaline (H), and is high for the five epochs after vehicle administration. Mice given cannabidiol after the first harmaline epoch (n = 10, circles) show a subsequent decline in tremor. Means and SEMs are shown. * $p<0.05$ ** $p<0.01$ *** $p<0.001$ Student's t-test.

3. Research Methods and Procedures

The mouse harmaline model of essential tremor will be used as described in our prior publiations (eg Martin et al., Mov Disord 2005). In brief, the mouse is placed on a platform fitted with a seismic detector and allowed to habituate before collecting motion power data. At all times the mouse is free to move within the confines of the tremor chamber. After injection of harmaline, 20 mg/kg i.p., tremor is allowed to develop and stabilize, then motion power again accessed for 15 minutes. Drugs are then administered, including CBD or other drugs suspected to suppress tremor, with or without administration of specific receptor antagonists. Motion power then is collected for five more 15-minute epochs. Controls are given vehicle. Harmaline tremor is associated with an increase in motion power at 10-16 Hz in mice. The tremor measure is motion power at 10-16 Hz divided by overall motion power at 1-32 Hz in order to control for activity level. Ratios of 0.1 to 0.3 are seen with normal acitivty whereas higher values indicate the presence of tremor at the 10-16 Hz frequency. C57BL/6 mice will be used, obtained from Jackson Labs.

<u>Experiment 1: Effect of CBD on harmaline tremor (Aim 1).</u>
Background: This experiment is to verify that CBD suppresses tremor in the harmaline mouse model.
Method: Pilot experiments will determine the doses of CBD that suppress temor by approximately 50% and 80%. In the formal experiment, on the completion of the harmaline-alone tremor epoch, mice will be administered either low dose CBD, high dose CBD, or vehicle (alcohol:cremophor:saline::1:2:37) i.p., then motion power accession resumed 10 minutes later, and continued for five 15-minute epochs. Each group will have 10 mice.
Discussion: This experiment is expected to show that CBD suppresses harmaline tremor compared to the vehicle-treated group, and will provide information on the dosages associated with moderate or marked suppression, and the time course of the effect.

<u>Experiment 2: Does CBD suppress tremor by activating the CB1 receptor? (Aim 2)</u>

Background: CBD has been reported to activate CB1 receptors indirectly by elevating the endogenous endocannabinoid AEA, and several actions of CBD have been reported to be CB1 receptor-dependent.
Method: Pilot studies will establish whether (a) the CB1 receptor agonist ACEA suppresses tremor at a dose below that reported to cause sedative effects (6 mg/kg), and if so what dose suppresses tremor by 80%, and (b) the CB1 antagonist AM251 has no effect on tremor when given as the sole agent. In the formal experiment, on completing the harmaline-alone epoch, mice will be administered vehicle or AM251, 6 mg/kg, followed by vehicle, high-dose CBD, or ACEA 10 minutes later, then motion power accession resumed 10 minutes after the second injection. Mice will be randomized to one of six groups: (1) vehicle plus vehicle; (2) vehicle plus high-dose CBD; (3) vehicle plus ACEA, (4) AM251 plus vehicle; (5) AM251 plus CBD; (6) AM251 plus ACEA. If ACEA has no effect on tremor, group 6 will be omitted. Sample size =10 per group. ACEA and AM251 will be dissolved in the same vehicle as with CBD.
Discussion: If CBD suppresses tremor via activation of CB! receptors, this effect will be blocked by the CB1 antagonist AM251, while the CB! agonist ACEA will also suppress tremor, an action also blocked by AM251.

Experiment 3: Does CBD suppress tremor by activating the CB2 receptor? (Aim 3)
Background: CBD has been reported to activate CB2 receptors indirectly by elevating the endogenous endocannabinoid AEA.
Method: Pilot studies will establish whether (a) the CB2 receptor agonist JWH133 suppresses tremor at a dose known not to cause sedative effects (15 mg/kg), and if so what dose suppresses tremor by 80%, and whether (b) the CB1 antagonist AM630 has no effect on tremor when given as the sole agent. In the formal experiment, on completing the harmaline-alone epoch, mice will be administered vehicle or AM630, 6 mg/kg, followed by vehicle, high-dose CBD, or JWH13310 minutes later, then motion power accession resumed 10 minutes after the second injection. Mice will be randomized to one of six groups: (1) vehicle plus vehicle; (2) vehicle plus high-dose CBD; (3) vehicle plus JWH133, (4) AM630 plus vehicle; (5) AM630 plus CBD; (6) AM630 plus JWH133. If JWH133 has no effect on tremor, group 6 will be omitted. Sample size =10 per group. AM630 and JWH133 will be dissolved in the same vehicle as with CBD.
Discussion: If CBD suppresses tremor via activation of CB2 receptors, this effect will be blocked by the CB2 antagonist AM630, while the CB2 agonist JWH133 will also suppress tremor, an action blocked by AM630.

Experiment 4: Does CBD suppress tremor by activating the 5HT1a receptor? (Aim 4)
Background: CBD is known to activate 5HT1a receptors..
Method: A pilot study will establish that the 5HT1a receptor antagonist WAY100635 does not affect tremor when given as the sole agent. In the formal experiment, after the harmaline-alone epoch, mice will be administered vehicle or WAY100635, 3 mg/kg, followed by vehicle or high-dose CBD 10 minutes later, then motion power accession resumed 10 minutes after the second injection. Mice will be randomized to one of four groups: (1) vehicle plus vehicle; (2) vehicle plus high-dose CBD; (3) WAY100635, 3 mg/kg, plus vehicle, (4) WAY100635 plus CBD.
Discussion: If CBD suppresses tremor via activation of 5HT1a receptors, this effect will be blocked by the 5HT1a antagonist WAY100635.

Experiment 5: Does CBD suppress tremor by activating the TRPV1 receptor? (Aijm 5)
Background: CBD is known to activate TRPV1 receptors both indirectly via AEA elevation and directly.
Method: A pilot study will establish that the TRPV1 receptor antagonist capsazepine does not affect tremor when given as the sole agent. In the formal experiment, after the harmaline-alone epoch, mice will be administered vehicle or capsazepine, 20 mg/kg, followed by vehicle or high-dose CBD 10 minutes later, then motion power accession resumed 10 minutes after the second injection. Mice will be randomized to one of four groups: (1) vehicle plus vehicle; (2) vehicle plus high-dose CBD; (3) capsazepine, 20 mg/kg, plus vehicle, (4) capsazepine plus CBD.
Discussion: If CBD suppresses tremor via activation of TRPV1 receptors, this effect will be blocked by the TRPV1 antagonist capsazepine.

Experiment 6: Does CBD suppress tremor via glycine receptors? (Aim 6)
Background: To address this question, we will employ a CBD derivative that is more selective as a positive allosteric modulator of glycine receptors, DH-CBD, and observe whether this compound suppresses tremor. In addition, we will assess whether the anti-tremor action of DH-CBD or of CBD is blocked by DD-CBD, which is a competitor for the allosteric binding site.

Method: Pilot experiments will determine whether (a) a dose of DH-CBD can be found that suppresses tremor by 80%, and (b) DD-CBD has any effect on tremor in doses at 50 mg/kg. If DD-CBD reduces tremor, the highest dose that does not affect tremor will be selected, otherwise 50 mg/kg will be used in subsequent experiments. In the formal experiment, mice will be injected with either vehicle or DD-CBD, upon completion of the first 20-minute harmaline epoch, injected 10 minutes later by vehicle, CBD, or DH-CBD, then permitted another 10 minutes before resuming motion power accession. Doses of CBD and DH-CBD will be those found to suppress tremor by approximately 80%. Mice will be randomized to one of six groups: (1) vehicle plus vehicle; (2) vehicle plus CBD; (3) vehicle plus DH-CBD; (4) DD-CBD plus vehicle; (5) DD-CBD plus DH-CBD; (6) DD-CBD plus CBD. All drugs will be dissolved as for CBD. Each group will have 10 animals. Note that if DH-CBD fails to suppress tremor, group 5 will be omitted.
Discussion: If CBD suppresses tremor through allosteric modulation of glycine receptors, it is anticipated that DH-CBD, which is more specific and potent for glycine receptors, will also suppress tremor, whereas DD-CBD will block the anti-tremor action of both DH-CBD and CBD.

4. Anticipated Results

We expect to confirm in Aim 1 that CBD suppresses tremor in the harmaline model of essential tremor, in keeping with preliminary clinical observations. In Aims 2 to 5 we will assess, using pharmacologic probes, whether the anti-tremor action of CBD is mediated by the cannabinoid CB1 or CB2 receptors (indirectly), or by 5HT1a or TRPV1 receptors. We suspect that it is less likely that the anti-tremor action is mediated by CB2 or 5HT1a receptors, nonetheless these possibilities will be assessed. It is possible that CB1 or TRPV1 receptor activation mediates tremor suppression. CBD in high doses causes somnolence in animals; animal research suggests that this effect of CBD is mediated by CB1 receptors. Knowledge that one of these receptors mediates tremor suppression would enable the formulation of strategies to minimize adverse events, such as development of allosteric modulators, which are generally better tolerated than orthosteric receptor ligands.

The most intriguing possibility would be a finding that CBD suppresses tremor through positive allosteric modulation of the brain glylcine receptor (Aim 6). Glylcine receptors are rich in the cerebellum, where tremor in ET is believed to be generated. Drugs specific for this action might exert considerable potency for tremor while being well tolerated. Investigators at the National Institute of Drug Abuse (NIDA) have devised a derivative of CBD, DH-CBD, that is specific for this allosteric binding site and avoids the sedating effects of CB1 activation. We will test DH-CBD as well as CBD in Aim 6.

In summary, we anticipate the proposed study will provide a rational basis for suppression of tremor by CBD, This information may justify a potential clinical trial of CBD for ET. More importan t, the study results will point the way towards the development of more selective, potent, and well-tolerated medications for ET.

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Budget

1. Salary support for biological technician
   300 hours x $30/hour basic salary plus 13% benefits = 10,170
2. Purchase cost of C57BL6 mice from Jackson Labs
   290 mice x 21.09 = 6,116
3. Housing cost of mice: 290 mice x $0.32 per diem x 40 days = 3712

Total: $19,998

Justification:

The biological technician, Pournima Kadam, MS, is experienced with the harmaline tremor model, drug injection, and data analysis. She will be available to work part-time on this project under the supervision of the PI, Adrian Handforth, MD.

After arrival, mice are quarantined, and allowed several weeks to grow to the size customarily used in our harmaline experiments. This is less expensive than buying mice at the higher weight.

Drugs for the study have already been purchased or, in the case of DH-CBD and DD-CBD, donated to our laboratory.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Adrian Handforth	Assistant Chief of Neurology VA Greater Los Angeles Healthcare System
eRA COMMONS USER NAME CHANDFORTH	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Queen's University, Kingston, Canada	B.S.	1972	Biochemistry
York University, Toronto, Canada	M.A.	1973	Psychology
McGill University, Montreal, Canada	M.S.	1975	Biochemistry
Queen's University, Kingston, Canada	M.D.	1979	Medicine
Queen's University, Kingston, Canada	F.R.C.P (C)	1984	Neurology

A. Personal Statement

I have performed clinical and basic research on essential tremor for almost 20 years. I have led or participated in clinical trials of levetiracetam, vagus nerve stimulation, topiramate, zonisamide, mefloquine and memantine for essential tremor. Our group set up the harmaline model in mice and has utilized it to study the effect of gap junction blockers, T-type calcium channel antagonists and GABA receptor agonists/modulators on tremor. Some of these investigations involved a genetic model of tremor involving mice with the alpha1 subunit of the GABA receptor deleted. Our work has been guided by hypotheses on tremor based on cerebellar circuits. With this combination of clinical exposure to patients with essential tremor and pharmacologic approaches to tremor in mouse models, we are well positioned to pursue themes in both the clinic and in the laboratory. Our interest in cannabidiol was sparked by observations by patients, and we wish to use the harmaline model to understand better how this drug suppresses tremor, knowledge that may eventually benefit those with essential tremor. My time allocation is as follows: Research: 46%, Clinical: 41%, Education: 10%, Administration: 3%.

B. Positions and Honors

Positions and Employment

1984 – 1987 Medical Research Council of Canada Fellowship, and Assistant Research Neurologist, University of California at Los Angeles, Los Angeles
1992 – 1997 Staff Neurologist VA Greater Los Angeles
1997 – Present Assistant Chief of Neurology, VA Greater Los Angeles

Other Experience and Professional Memberships

1980 Member, American Academy of Neurology
1998 Member, Movement Disorders Society
2012 Member, Medical Advisory Board, International Essential Tremor Foundation

C. Selected Peer-reviewed Publications (Selected from 45 peer-reviewed publications)

Most relevant to the current application

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D. Research Support

Ongoing Research Support

2/2014- present Veterans Affaires Merit Award PI: Handforth
The purpose of this study is to use pharmacologic probes and mouse genotypes to try to identify the low-dose alcohol target for tremor suppression.

2004 – present PI: Medtronic-sponsored trial of anterior thalamus stimulation for epilepsy
This is a multicenter pivotal trial of deep brain stimulation for intractable epilepsy.

Completed Research Support

2/2010-2013 International Essential Tremor Foundation. PI Handforth
This grant provided pilot data that enabled the VA grant to identlfy the GABA receptor subtype that mediates tremor suppression.

2/2012-2/2013 Ralph M. Parsons Foundation: Essential Tremor Research Program
PI Handforth. The purpose of this grant was to provide initial data on the role of delta GABA receptors in affecting tremor in the harmaline model. This grant helped provide pilot data for the present proposal.

2005 – 2008 PI: Ralph M. Parsons Foundation: Essential Tremor Research Program
This project supported work on the role of T-type calcium channel antagonists in tremor.

2006 – 2008 Co-Investigator: International Essential Tremor Foundation: Rote of T-type calcium channels in tremor expression. This study investigated the role of the T-type calcium channel in the xpression of tremor in essential tremor models in mice.

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CONFLICT OF INTEREST QUESTIONNAIRE
Grant Proposal Submissions

Pursuant to the purposes and interests of the policy adopted by the IETF Board of Directors requiring disclosure of certain interests, a copy of which has been furnished to me, I hereby state that I or relatives have the following affiliations or interests and have taken part in the following transactions which, when considered in conjunction with my relationship to the International Essential Tremor Foundation (IETF) might create or be a conflict of interest. (Write "none" where applicable).

1. Advisory Board or Panel Affiliation

   IETF Medical Advisory

2. Consulting, Speakers Bureau or Contractual Services

   None

3. Research/Grant Support

   Medtronic

4. Financial or Material Support not otherwise listed.

   None

I hereby acknowledge the information given is complete and accurate to the best of my knowledge and belief. I understand that failure to accurately disclose a potential interest may cause revocation of my grant award if approved. I also understand that if any of the above circumstances change, that I am to complete a new questionnaire.

Adrian Handforth, MD — 2/25/2015

Signature — Date

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Signature — Date

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