

Treatment of Essential Tremor with Long-Chain Alcohols: Still Experimental or Ready for Prime Time?

Dietrich Haubenberger^{1,2*}, Fatta B. Nahab³, Bernhard Voller^{1,2} & Mark Hallett²

¹ Department of Neurology, Medical University of Vienna, Vienna, Austria, ² Human Motor Control Section, Medical Neurology Branch, National Institutes of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland, United States of America, ³ Movement Disorders Center, Department of Neurosciences, University of California San Diego, La Jolla, California, United States of America

Abstract

Aim: To review current literature on long-chain alcohols and their derivatives as novel pharmacotherapy for the treatment of essential tremor (ET).

Background: Currently available and recommended pharmacotherapies for ET are often limited by suboptimal treatment effects, frequent adverse effects, and drug interactions. While ethanol is reported to profoundly decrease tremor severity in the majority of patients with ET, preclinical experience suggests that long-chain alcohols such as 1-octanol might lead to a comparable tremor reduction without ethanol's typical side effects of sedation and intoxication. Here, we review the literature on the first clinical trials on 1-octanol and its metabolite octanoic acid (OA) for the treatment of ET.

Methods: The literature on preclinical and clinical trials on long-chain alcohols as well as OA was reviewed and summarized, and an outlook given on next phases of development.

Discussion: 1-octanol was demonstrated to be safe and effective in a double-blind, placebo-controlled low-dose trial, and open-label data showed excellent tolerability and dose-dependent efficacy up to 128 mg/kg. Despite 1-octanol's efficacy, its future viability as an effective therapy is limited by its pharmacological properties that require large volumes to be orally administered. Pharmacokinetic data indicate that OA is the active metabolite of 1-octanol. Preclinical efficacy data for OA are positive, and human pilot data demonstrated excellent safety as well as efficacy in secondary outcome measures of tremor amplitudes. OA also has more favorable pharmacological properties for drug delivery; hence, OA may be worth developing as a pharmaceutical.

Keywords: Essential tremor, alcohol, ethanol, octanol, octanoic-acid, harmaline-model

Citation: Haubenberger D, Nahab FB, Voller B, et al. Treatment of essential tremor with long-chain alcohols: still experimental or ready for prime time? *Tremor Other Hyperkinet Mov* 2014; 4. doi: 10.7916/D8RX991R

*To whom correspondence should be addressed. E-mail: dietrich.haubenberger@meduniwien.ac.at

Editor: Elan D. Louis, Columbia University, United States of America

Received: October 10, 2013 **Accepted:** December 31, 2013 **Published:** February 5, 2014

Copyright: © 2014 Haubenberger et al. This is an open-access article distributed under the terms of the Creative Commons Attribution–Noncommercial–No Derivatives License, which permits the user to copy, distribute, and transmit the work provided that the original author(s) and source are credited; that no commercial use is made of the work; and that the work is not altered or transformed.

Funding: Clinical trials on 1-octanol and OA were conducted at the NINDS intramural research program through support by the NINDS research program, the Austrian Science Fund (D.H.) as well as a Cooperative Research and Development Agreement (CRADA) with Manhattan Pharmaceuticals (B.V.). D.H. received research support through the NINDS Intramural Research Program and the Austrian Science Fund FWF (Erwin Schroedinger Fellowship, Project number J2783-B09).

Financial Disclosures: F.B.N. receives funding support from the National Institute of Neurological Disorders and Stroke (1R01NS073683-01A1). D.H. serves as member of the Medical Advisory Board of the International Essential Tremor Foundation and received speaker honoraria and conference support from Ipsen and UCB. F.B.N. received support from the University of Miami Clinical and Translational Science Institute, the National Center for Advancing Translational Sciences and the National Institute on Minority Health and Health Disparities (1UL1TR000460); an educational grant from Medtronic, Inc; receives royalties from Springer Publishing; and is a reviewer for the Veterans Administration. B.V. was sponsored by Manhattan Pharmaceuticals Inc. He worked as a contractor and as a Special Volunteer at NIH/NINDS in accordance with a Cooperative Research and Development Agreement (CRADA) with Manhattan Pharmaceuticals on a trial not included in this review. M.H. serves as Chair of the Medical Advisory Board for and receives funding for travel from the Neurotoxin Institute; he serves as Chair of the Medical Advisory Board of the Benign Essential Blepharospasm Foundation and Chair of the Medical Advisory Board of the International Essential Tremor Foundation; he has received honoraria and/or funding for travel for lectures or educational activities not funded by industry; he serves on Editorial Boards for *Clinical Neurophysiology*, *Acta Neurologica Scandinavica*, *Journal of Clinical Neurophysiology*, *Italian Journal of Neurological Sciences*, *Medical Problems of Performing Artists*, *Annals of Neurology*, *Neurology and Clinical Neurophysiology*, *The Cerebellum*, *NeuroTherapeutics*, *Current Trends in Neurology*, *Faculty of 1000 Medicine*, *Brain Stimulation*, *Journal of Movement Disorders (Korea)*, and *World Neurology*; he may accrue revenue on US Patent #6,780,413 B2 (issued: August 24, 2004): immunotoxin (MAB-Ricin) for the treatment of focal movement disorders; US Patent #7,407,478 (issued: August 5, 2008): coil for magnetic stimulation and methods for using the same; he receives royalties from publishing from Blackwell Publisher, Cambridge University Press, Springer Verlag, Taylor

& Francis Group, Oxford University Press, John Wiley & Sons, and Elsevier; he has received license fee payments from the NIH (from Brainsway) for licensing the patent for the H-coil. M.H.'s research at the NIH is largely supported by the NIH Intramural Program. Supplemental research funds come from Manhattan Pharmaceutical Company via a CRADA with the NIH, and the Kinetics Foundation via a Clinical Trials Agreement (CTA) with the NIH.

Conflict of Interest: The authors report, that regarding the trials discussed in the review, there are no conflicts of interest in any of the authors.

Introduction

Essential tremor (ET) is a common movement disorder with a prevalence in the general population between 0.4% and 3.9%.¹ ET is a slowly progressive disease with 73% of patients describing disabilities in multiple functional domains including eating, drinking, writing, and body care.²

Since there is currently no curative therapy available for ET, medical agents including propranolol and primidone as well as deep brain stimulation of the ventral intermediate nucleus (VIM) are symptomatic therapeutic options. However, the clinical effects of these first-line drugs are often limited by contraindications and intolerable side effects, particularly in elderly patients,³ and many patients are not keen on surgery.

Ethanol and essential tremor

One characteristic observation in ET is that up to 74% of affected subjects report a significant reduction in tremor intensity after the administration of small amounts of ethanol.⁴⁻⁶ It should be noted that this observation is based on subjective data only, while objective data on the ethanol response in ET is scarce. In a study by Knudsen et al.,⁷ a standardized oral ethanol challenge led to an improvement of up to 50% of hand tremor scores in 25 patients, which lasted up to 3 h. It was also demonstrated by the same group that after ethanol, ataxia scores and number of missteps during tandem gait improved equally in patients with ET, suggesting a beneficial effect of ethanol in ET patients beyond the actual tremor.⁸ The evidence for a central effect of ethanol stems from neurophysiological studies using weighted accelerometry demonstrating a significant reduction of the central tremor component following standardized oral ethanol administration.⁹ Furthermore, the specificity of the effect was demonstrated to be mediated by the central nervous system (CNS), as an effect was seen after systemic intravenous administration, without effect after intra-arterial perfusion in a vascularly isolated limb of patients with ET.¹⁰ The tremor-reducing effect on the central component was demonstrated to be specific for ethanol, as diazepam showed no effect. Furthermore, this finding demonstrated that ethanol acted specifically on a central tremor oscillator at plasma ethanol levels of 0.05 g/dL, independent of effects mediated through relaxation or sedation seen with diazepam.⁹

Several hypotheses exist regarding the mechanism of ethanol's effect in ET.

First, ethanol has been suggested to decrease the neuronal firing rate of the inferior olive (IO) and may therefore lead to a reduction in hypersynchronous bursting activity within Mollaret's triangle connecting the red nucleus, the IO, and the cerebellum, with further

propagation along the cerebello-thalamo-cortical loop.¹¹ There are two possible derangements. First, this mechanism is thought to be mediated through modulation of low-threshold calcium channels in the IO that are responsible for rhythmical cellular firing.

There can be hyperfunctioning of the low-threshold calcium channel in the inferior olivary cells leading to oscillatory neuronal activity.¹² Notably, ethanol in low doses has been reported to increase T-type currents of low-threshold calcium channels; however, at toxic levels data show ethanol is blocking these channels.¹³ While the relevance of low-threshold calcium channels has been demonstrated in the harmaline model of ET, the role in humans remains to be elucidated, as in humans lesions affecting the efferent cerebellar pathways (such as strokes) might abolish tremor in ET patients, but no "curative" lesions affecting the IO complex have been reported so far.¹⁴

Contrary to the hypothesis of ethanol as a depressor of neuronal IO firing, a study using different methods of anesthesia by Rogers et al.¹⁵ suggested that the depressing effect might in fact be due to the specific anesthesia used in the original experiment by Harris and Sinclair (urethane),¹¹ as ethanol under this varying anesthesia condition actually led to an increase in the IO single-unit firing rate.

Second, the neuronal rhythmic discharges within the IO may be hypersynchronized by electrical coupling mediated through gap junctions.¹⁶ These gap junctions connect and therefore electrically couple dendritic spines in synaptic glomeruli within the IO, which are thought to be central for the IO's oscillatory activity. Gamma-aminobutyric acid (GABA)ergic terminals in the synaptic glomeruli have shown to decrease the extent of electric coupling.¹⁷ By blocking connexin 36, a crucial gap junction protein within the IO, mice still develop harmaline-induced tremor although with decreased tremor coherence.^{18,19} This suggests that the profound tremor-reducing effect of gap junction blockers such as mefloquine in harmaline mice may act via different gap junctions, not containing connexin 36.²⁰

Furthermore, ethanol's agonism on GABA-receptors has been implicated as a correlate of its tremor-suppressing properties. GABA is the main inhibitory neurotransmitter, with GABA_A receptors being expressed either synaptically (90%) or extrasynaptically (10%). Synaptic receptors mediate phasic inhibition, whereas tonic inhibition is mediated via extrasynaptic receptors,²¹ which are thought to be physiologically activated by "overspill" of synaptically released GABA.²² GABA_A receptors form pentamers containing two alpha, two beta, and either one gamma or one delta subunit.²³ The majority of GABA_A receptors contain a gamma subunit, are expressed synaptically, and are benzodiazepine sensitive. Receptors containing a delta subunit are mainly expressed extrasynaptically and are non-sensitive to benzodiazepines but in contrast show a very high sensitivity

to GABA and ethanol, and therefore might play a role in facilitating a GABAergic effect of ethanol.²⁴ Delta subunits containing receptors form pentamers with alpha1, 4, and 6 subunits. While alpha1delta receptors can only be found in the hippocampus, alpha6delta receptors are exclusively expressed in cerebellar granule cells, and alpha4delta receptors more widespread in the cerebral cortex, thalamus, and the cerebellum.²⁵ The major role of the extrasynaptically located alpha6delta receptor in determining the response to ethanol has been confirmed in a recombinant study where the R100Q polymorphism of the gene coding for the alpha6 subunit was shown to enhance sensitivity to ethanol.²⁶ While alpha1 subunit knockout mice have been suggested to exhibit a phenotype resembling ET including ethanol responsiveness, a screen for variants in the gene coding for the alpha1 subunit showed no genetic differences between ET subjects and controls.^{27,28} Genetic alpha6 subunit variants have been associated with different levels of response to ethanol in humans.²⁹

Although disputed by others,³⁰ data from a prospective ET brain bank study showed a reduced cerebellar Purkinje cell number in over 75% of patients compared with control brains.³¹ With GABA being the main neurotransmitter of Purkinje cell projections, ET has been suggested to be a “Purkinjopathy”, also characterized by increased prevalence of axonal swellings (“torpedoes”) of Purkinje neurons in ET brains.^{32,33}

Summarizing the evidence on the ethanol effect in ET, although there are several hypotheses on the potential mechanisms of action, it is important to point out that insights gained from the harmaline model are not certain to reflect the human pathophysiologic mechanism in ET. Specifically, T-type calcium channels and non-connexin 36 gap junctions in CNS regions other than the IO, as well as the GABAergic system, represent relevant targets to be further investigated.

Methods

The relevant literature on preclinical and clinical trials of long-chain alcohols and OA were identified via a Pubmed search. Search terms were “octanol”, “1-octanol”, “octanoic acid”, and “caprylic acid”, with searches limited to clinical trials. Furthermore, the terms “ethanol” and “alcohol” were searched in conjunction with “essential tremor”. The time frame of papers to be included was limited by the time point of the writing of this manuscript (October 2013). Because of limited relevance to this review, trials involving octanoic acid as a ¹³C-labeled substance to investigate gastric emptying were excluded from the search. Secondary literature was followed up, reviewed, and discussed here if found relevant to the topic of this manuscript. Here we provide a summary of the review as well as an outlook given on the next phases of development.

Results and discussion

Long-chain alcohols

Alcohols ranging from methanol (CH₄O) to decanol (C₁₀H₂₂O) were first studied using an *in vitro* model of guinea-pig IO neurons, where octanol was described to be a potent antagonist of IO low-threshold calcium channels.³⁴ In a further step, several octanol

isomers, including 1-octanol, were first studied *in vivo* using the harmaline-induced rodent model of ET. All isomers, at varying effective doses, demonstrated a potent effect in reducing harmaline-induced tremor.³⁵ In a comparative study on 1-octanol and 1-heptanol, both long-chain alcohols, reduced harmaline-induced tremor in mice at a dose of 350 mg/kg after intraperitoneal administration, with 1-octanol exhibiting a superior efficacy profile than 1-heptanol due to a longer duration of the effect.²⁰

1-Octanol: preclinical evidence

The eight-chain alcohol 1-octanol is hypothesized to be metabolized by octanol dehydrogenase, a member of the alcohol dehydrogenase family of enzymes, to an aldehyde and then a carboxylic acid that is either oxidized completely to carbon dioxide and water or excreted as an ether-glucuronide after direct conjugation with glucuronic acid.³⁶

1-Octanol has been demonstrated to block the low-threshold calcium channel in the IO and thalamus *in vitro*.^{34,37} The maximum tolerated dose preclinically in harmaline mice after intraperitoneal administration using the straight-wire test was 1,000 mg/kg.³⁸ The Food and Drug Administration (FDA) food additive safety profile on 1-octanol lists lethal acute toxicity levels in rodents (LD₅₀) ranging from 1,790 to 15,000 mg/kg.

1-Octanol: clinical trials

1-Octanol was first chosen for clinical trials due to its superior efficacy and safety profile in animal model testing, and the fact that 1 mg/kg dosing was considered to be safe in humans, as defined by the Council of Europe. 1-Octanol is approved as a food flavoring substance by the FDA.

The first clinical trial in ET was conducted using a low dose of 1 mg/kg in 12 patients.³⁹ A single oral dose of 1-octanol showed a moderate effect in reducing tremor up to 90 min after administration, measured by accelerometry, using a double-blind, placebo-controlled design. 1-Octanol was well tolerated and safe at this dosage. Three patients (two in the octanol group, one in the placebo group) complained of headaches occurring after the completion of the study. In all three patients, the headache lasted for less than 2 h and responded to acetaminophen. No changes in vital signs or liver function tests were detected. No signs of intoxication were observed.

The second protocol using 1-octanol was an open-label dose escalation study to find the maximal tolerated oral dose of 1-octanol.⁴⁰ Octanol doses were escalated up to 64 mg/kg without evidence of intoxication, though subjects had a sensation of sedation at maximal doses. Efficacy was found at all dosages, and a trend toward a dose response was noted. Safety profiles showed no significant adverse events, with some mild side effects. Two subjects had a self-limited headache following drug administration, four subjects noted a taste associated with the drug approximately 1 h after ingestion, four subjects described a transient mild asthenia without signs of intoxication, and two subjects had a prolonged feeling of lethargy at 64 mg/kg lasting for several hours. Single reports of nausea, dry mouth, calcium oxalate crystals in the urine, and urinary tract

infections were present, and in the case of the last two were likely unrelated. No laboratory abnormalities or electrocardiogram (EKG) changes were noted.⁴⁰

The most recent 1-octanol protocol (clinicaltrials.gov ID: NCT00102596) investigated the pharmacokinetic properties of two different oral formulations of 1-octanol in 15 patients with ET.⁴¹ The first formulation consisted of 1-octanol adsorbed to microcrystalline cellulose and fine particle silica and encapsulated; the second formulation consisted of a soft-gel capsule containing 1-octanol embedded in soybean oil.⁴¹

This protocol was designed as a three-phase unblinded inpatient study of adults with ET receiving weight-adjusted oral dosages of two different formulations of 1-octanol in a crossover fashion. Phase 1 of the study was designed to develop octanol and OA detection assays using high-performance liquid chromatography. Five subjects in phase 1 received daily escalating dosages (1–64 mg/kg) of a single 1-octanol formulation. In phase 2, 10 subjects received one of the two formulations at 64 mg/kg during two inpatient days separated by one washout-day. In phase 3, two patients received a high-dose challenge of both formulations of 1-octanol (128 mg/kg).

Plasma concentrations of both 1-octanol and OA were detectable as early as 5-min post dose. While OA concentrations showed a dose response, 1-octanol remained at very low basal levels until the 64 mg/kg dose. The OA plasma half-life was 73.6 min. In phase 3 of the study, after the administration of a high dose of 1-octanol (128 mg/kg), observed OA plasma levels followed a linear relation compared with lower doses of 1-octanol. These findings suggested that 1-octanol is rapidly converted to OA, which might then act as the active metabolite. Efficacy was measured using objective digital tremor spiral analysis.⁴² Spiral tremor measurements showed a 32% reduction in tremor amplitudes at 90 min with significant tremor improvement up to 180 min after administration. The safety profile of 1-octanol up to 128 mg/kg resembled prior studies with non-serious side effects being mild and self-limiting. The most frequent adverse event was taste change, which was reported by eight subjects (38%), followed by headache, heartburn, and bloating (each five subjects, 24%). Nausea and dry mouth were reported by four subjects (19%), and three subjects reported constipation (14%). Two serious adverse events were not related to the study drug. Again, no signs of intoxication were noted at either dose level.

Octanoic acid

OA (synonym: caprylic acid) is a fatty acid with an eight-carbon chain, which has been shown to inhibit gap junction permeability in cultured rat astrocytes.⁴³ Whether this observation is relevant to explain a potential effect in ET remains uncertain, as it is not known whether OA also blocks neuronal gap junctions. OA occurs naturally in palm and coconut oils, as well as in human and bovine milk, and is part of commercially available nutritional supplements (Caprinol®, Capryl®). After absorption in the intestinal mucosa and entering the portal venous system, the hepatic metabolism of OA involves catabolism via β -oxidation to acetyl coenzyme A (CoA) with

subsequent entry into the Krebs cycle. Extrahepatic metabolism of OA involves oxidation into CO₂ within extrahepatic tissues.^{44,45}

The FDA has registered OA as a food additive and adjuvant of food products, and assigned it “GRAS” (Generally Recognized as Safe) status. Currently, OA is mainly used as a food and cosmetic additive as well as an assessment method of gastric emptying (¹³C OA breath test). The Council of Europe lists OA as a flavoring substance with an upper limit of 50 mg/kg in food.⁴⁶ Orally administered OA shows a bioavailability of nearly 100%.⁴⁷ In the rat, OA permeated the blood–brain barrier, with 94% of peripherally injected OA being measurable in the brain.⁴⁸ To our knowledge, there are no data in the literature on the elimination profile of OA from the CNS. In a study of acute oral toxicity in rats, the LD₅₀ was 10,080 mg/kg.⁴⁹

Octanoic acid: experience from human exposure

There is considerable data available on human exposure of OA. In humans, according to a single-dose administration paradigm of medium-chain fatty acids, a dietary consumption of up to 710 mg/kg was considered safe.⁵⁰ In a clinical trial including a control group of healthy volunteers, a total dose of 3,600 mg OA was administered via intraduodenal infusion, and no clinical side effects were reported.⁵¹ OA was furthermore studied as a component of a ketogenic diet as a treatment strategy in children with intractable epilepsy, with a duration of chronic administration for up to 2 years.^{52,53} An OA-containing diet was administered on a daily basis as an emulsion with the goal that 60% of the daily energy requirement was supplied by the diet. Fifty children were included in the study, with 44 children tolerating the diet. Reported side effects were diarrhea and abdominal pain, which were alleviated by temporary dose reduction or intake together with food. “Optimal” plasma levels of OA intended by the authors was a target of 90 μ g/mL peak plasma concentration (C_{max}), with the actual measured C_{max} values ranging from 98.2 to 258.9 μ g/mL. Compared with the available pharmacokinetic data on OA in essential tremor, these plasma levels were 75–200 times higher than the C_{max} we measured in the ET trial using 1-octanol. The dose vs. plasma concentration relation was suggested to follow a linear relationship.⁵²

Further human data on OA stem from a study administering OA as a formula to six premature infants. OA was administered orally in doses ranging from 1.3 to 1.7 g/kg/d (mean 1.5 ± 0.2 g/kg/d) via a medium-chain triglyceride diet over a period of at least 10 days. The goal of this study was to investigate the metabolism of medium-chain triglycerides in infants. The authors demonstrated the conversion of OA into long-chain saturated fatty acids. The study did not mention any adverse events.⁵⁴ In a study of 23 cachectic patients, OA given orally at a dose of 2.8 g daily over 2 weeks increased appetite scores, body weight, and levels of total serum protein and albumin, with no negative impacts on fasting glucose, total cholesterol, or triglycerides. The aim of the study was to investigate the effect of OA on the orexigenic hormone ghrelin, and demonstrated that OA led to an increase in acyl ghrelin.⁵⁵ High levels of OA were measured in patients with a deficiency of medium-chain acyl-CoA dehydrogenase (OMIM

#607008), an autosomal recessive inherited disorder of infancy and early childhood leading to metabolic acidosis, hypoglycemia, lethargy, coma, and if left unrecognized led to death in 25% of patients during their first crisis.^{56,57} Regarding potential drug interactions, it has been shown that high levels of OA can displace warfarin and non-steroidal anti-inflammatory agents from albumin binding in human serum.⁵⁸

Octanoic acid in ET: preclinical evidence

Because of OA's presumed role as 1-octanol's primary metabolite and its biochemical properties, OA itself was hypothesized to act as a potential therapeutic agent in ET. In the harmaline-induced mouse-model of ET, OA showed a dose-dependent effect in reducing tremor intensities, starting at 300 mg/kg administered intraperitoneally with a maximum tolerated dose of 1,500 mg/kg. At therapeutic doses no toxicity was observed, especially no signs of sedation or intoxication.³⁸

Octanoic acid: first experience in ET

The aim of the first study of OA in ET was to examine the safety and efficacy of a single oral OA dose in a double-blind, randomized, placebo-controlled, crossover design (NCT00848172).⁵⁹ Nineteen patients with ethanol-responsive ET were included in the protocol. All subjects received a dose that was defined as being safe according to available toxicity data (4 mg/kg) and were monitored closely during the total inpatient study phase of 3 days (day 0, baseline; days 1–2, active study days). OA and placebo were administered on consecutive study days in a randomized sequence. The primary outcome measure for this study was the effect on tremor power of the dominant hand, 80 min after administration of the study substance compared with placebo. Tremor power was measured using accelerometry with loading to test the central tremor component. Secondary outcome measures included recordings of tremor power as measured by accelerometry at multiple other time points up to 300 min after administration. The change in tremor severity documented by digital spiral analysis, safety assessment (laboratory testing, documentation of vital signs, adverse events questionnaire, and intoxication scale), and pharmacokinetic sampling acted as a further secondary outcome parameter.

Efficacy endpoints measured with tremor accelerometry did not meet the primary endpoint (reduced tremor power of the dominant hand 80 min after administration, compared with placebo). However, secondary efficacy measures showed a significant benefit over placebo at later time points, starting at 150 min. At the last observational time point, 300 min, there was still a significant reduction in tremor power compared with baseline.

Pharmacokinetic analysis of OA showed a t_{max} at 72.8 min, a relatively large volume of distribution (389 L), and an elimination half-life of 83.5 min. The elimination did not entirely follow first-order kinetics, suggesting the presence of a second compartment. The mean C_{max} after administration of 4 mg/kg was 1,288.4 ng/mL, which is close to the C_{max} of OA that was measured after the administration of 4 mg/kg of 1-octanol.

Safety analysis showed that the dose was safe and well tolerated. There were no serious adverse events related to OA, with non-serious

adverse effects being mild, self-limiting, and equally present after OA and placebo. Two serious adverse events were classified as not related to OA (food poisoning with isolated troponin I elevation after placebo, and bleeding from the insertion site of a peripherally inserted central venous catheter after premature removal of pressure dressing). There were no significant abnormalities noted on vital signs, EKG, or laboratory measures throughout the study.

Summary and outlook

With pharmacotherapy in ET often being limited by insufficient efficacy, intolerable side effects, and potential drug interactions, novel treatments for ET are strongly needed. While the ethanol effect in ET is still not fully understood and currently under investigation, it is clear that the majority of patients experience a clinically significant effect of tremor reduction even after low doses of ethanol consumption, often exceeding the effects of pharmacological treatments such as propranolol and primidone.

With the detailed mechanism of effect of ethanol in ET still to be determined, promising preclinical data led to the further development of long-chain alcohols as potential treatment agents in ET. It is however important to point out that ethanol shows different (lower) affinity to target structures than longer-chain alcohols such as 1-octanol. It is therefore not necessarily the case that ethanol and 1-octanol act via the same mechanism. Also, 1-octanol might act not via one, but multiple mechanisms (i.e., blockage of gap junction, T-type calcium channels, GABA-receptor interaction).

The fact that the 1-octanol and OA studies so far required participants to exhibit a beneficial response to ethanol therefore stems from a debatable assumption of similar pathways facilitating the effect. It is however also important to point out that the current concept on the proportion of ET patients responding beneficially to ethanol, or not, is likely outdated, as these data stem from purely subjective reports. Objective data from larger-scale populations are still pending, to investigate whether differences in ethanol response can be objectively delineated and whether therefore a concept of two separate ET endophenotypes based on ethanol response can be sustained. However, in the light of the current diagnostic uncertainty and significant disagreement in the field on the “core” ET phenotype, a limitation to objective ethanol responders might be justified for early stage clinical trials to achieve a cohort exhibiting a more homogeneous phenotype.

With three clinical trials available on efficacy, safety, and pharmacokinetic properties of 1-octanol, the main results can be summarized as 1-octanol being safe and well tolerated in doses up to 128 mg/kg. The most common adverse event was mild and transient dysgeusia, with patients reporting a distinct taste of orange peel, which was to be expected as 1-octanol as natural flavoring substance is present in orange peel. In terms of efficacy, all studies demonstrated a significant treatment effect of 1-octanol, though it should be noted that only the first, low-dose study was a double-blind, placebo-controlled design. One major finding of the 1-octanol trials was the detection of OA as an active metabolite with a significant plasma response after the administration of 1-octanol. The feasibility of 1-octanol was furthermore questioned, not only because the distinct taste would make

sufficient blinding challenging, but also because of the relatively large volumes to be administered orally at doses of 64 and 128 mg/kg: even with the formulation using the highest 1-octanol concentration (gel capsule containing 800 mg 1-octanol), a patient weighing 78 kg who took part in the highest dose group of 128 mg/kg had to swallow 12 capsules as a one-time dose.

OA itself showed an excellent safety and efficacy profile in preclinical testing and during human exposure as a nutritional agent, even at high doses and in vulnerable subjects such as preterm infants. While OA was well tolerated in a pilot study using a low dose (4 mg/kg), the primary efficacy outcome was not met, with OA not being different from placebo in reducing tremor 80 min after administration. However, the study design included several secondary efficacy outcomes, which showed a significant effect on tremor at later time points. The observation of a peak in plasma levels at 73 min being dissociated from a clinical effect manifesting at 150 min and later, in conjunction with an elimination profile compatible with a second compartment, suggests that the second compartment is likely the CNS, where the clinical effect is manifesting after distribution of the compound across the blood–brain barrier, potentially explaining the lag of a clinical efficacy peak following the plasma peak. While the effect was evident using highly sensitive tremor accelerometry, other methods better reflecting daily-life activities such as digital spiral analysis were not different between OA and placebo. As this was a low-dose study, it was assumed that the effect at 4 mg/kg was still small and not yet translating into a clinically relevant benefit. Therefore, a dose escalation study, with the goal of defining a maximum tolerated dose with doses up to 128 mg/kg, was initiated (NCT01468948), with the results at the time of this review still pending. Further studies are needed on the effect of OA when administered continuously (e.g., twice daily, three times daily, etc.), on the further characterization of OA's pharmacokinetic profile at higher doses, and the optimization of the drug's formulation.

To conclude, despite its efficacy and safety, 1-octanol itself does not seem a feasible candidate for further development due to the relatively large volumes to be administered when formulated in capsules for oral administration, as well the finding of OA as the active metabolite. Although OA's mechanism of action in ET is still unknown, the therapeutic potential of OA in ET can be considered as significant, due to promising preclinical and early-stage clinical trial data. However, a clinically relevant effect translating into a reduced burden of tremor in patients' daily lives still remains to be demonstrated, and additional phase 2 data on safety and efficacy in a long-term administration setting are necessary, in order to keep OA moving forward towards prime time.

References

1. Louis ED, Ottman R, Hauser WA. How common is the most common adult movement disorder? Estimates of the prevalence of essential tremor throughout the world. *Mov Disord* 1998;13:5–10, doi: <http://dx.doi.org/10.1002/mds.870130105>.
2. Louis ED, Barnes L, Albert SM, et al. Correlates of functional disability in essential tremor. *Mov Disord* 2001;16:914–920, doi: <http://dx.doi.org/10.1002/mds.1184>.
3. Deuschl G, Raethjen J, Hellriegel H, Elble R. Treatment of patients with essential tremor. *Lancet Neurol* 2011;10:148–161, doi: [http://dx.doi.org/10.1016/S1474-4422\(10\)70322-7](http://dx.doi.org/10.1016/S1474-4422(10)70322-7).
4. Deuschl G, Wenzelburger R, Löffler K, Raethjen J, Stolze H. Essential tremor and cerebellar dysfunction clinical and kinematic analysis of intention tremor. *Brain* 2000;123:1568–1580, doi: <http://dx.doi.org/10.1093/brain/123.8.1568>.
5. Koller WC, Busenbark K, Miner K. The relationship of essential tremor to other movement disorders: report on 678 patients. Essential Tremor Study Group. *Ann Neurol* 1994;35:717–723, doi: <http://dx.doi.org/10.1002/ana.410350613>.
6. Lou JS, Jankovic J. Essential tremor: clinical correlates in 350 patients. *Neurology* 1991;41:234–238, doi: http://dx.doi.org/10.1212/WNL.41.2_Part_1.234.
7. Knudsen K, Lorenz D, Deuschl G. A clinical test for the alcohol sensitivity of essential tremor. *Mov Disord* 2011;26:2291–2295, doi: <http://dx.doi.org/10.1002/mds.23846>.
8. Klebe S, Stolze H, Gensing K, Volkmann J, Wenzelburger R, Deuschl G. Influence of alcohol on gait in patients with essential tremor. *Neurology* 2005;65:96–101, doi: <http://dx.doi.org/10.1212/01.wnl.0000167550.97413.1f>.
9. Zeuner KE, Molloy FM, Shoge RO, Goldstein SR, Wesley R, Hallett M. Effect of ethanol on the central oscillator in essential tremor. *Mov Disord* 2003;18:1280–1285, doi: <http://dx.doi.org/10.1002/mds.10553>.
10. Growdon JH, Shahani BT, Young RR. The effect of alcohol on essential tremor. *Neurology* 1975;25:259–262, doi: <http://dx.doi.org/10.1212/WNL.25.3.259>.
11. Harris DP, Sinclair JG. Ethanol depresses inferior olive neurones and reduces Purkinje cell complex spike activity evoked by cerebral cortical stimulation. *Gen Pharmacol* 1984;15:455–459, doi: [http://dx.doi.org/10.1016/0306-3623\(84\)90199-X](http://dx.doi.org/10.1016/0306-3623(84)90199-X).
12. Llinas R, Yarom Y. Properties and distribution of ionic conductances generating electroresponsiveness of mammalian inferior olivary neurones in vitro. *J Physiol* 1981;315:569–584.
13. Mu J, Carden WB, Kurukulasuriya NC, Alexander GM, Godwin DW. Ethanol influences on native T-type calcium current in thalamic sleep circuitry. *J Pharmacol Exp Ther* 2003;307:197–204, doi: <http://dx.doi.org/10.1124/jpet.103.053272>.
14. Dupuis MJ, Evrard FL, Jacquerye PG, Picard GR, Lermen OG. Disappearance of essential tremor after stroke. *Mov Disord* 2010;25:2884–2887, doi: <http://dx.doi.org/10.1002/mds.23328>.
15. Rogers J, Madamba SG, Staunton DA, Siggins GR. Ethanol increases single unit activity in the inferior olivary nucleus. *Brain Res* 1986;385:253–262, doi: [http://dx.doi.org/10.1016/0006-8993\(86\)91071-1](http://dx.doi.org/10.1016/0006-8993(86)91071-1).
16. Sotelo C, Llinas R, Baker R. Structural study of inferior olivary nucleus of the cat: morphological correlates of electrotonic coupling. *J Neurophysiol* 1974;37:541–559.
17. Onizuka M, Hoang H, Kawato M, et al. Solution to the inverse problem of estimating gap-junctional and inhibitory conductance in inferior olive neurons from spike trains by network model simulation. *Neural Netw* 2013;47:51–63, doi: <http://dx.doi.org/10.1016/j.neunet.2013.01.006>.

18. Placantonakis DG, Bukovsky AA, Zeng XH, Kiem HP, Welsh JP. Fundamental role of inferior olive connexin 36 in muscle coherence during tremor. *Proc Natl Acad Sci U S A* 2004;101:7164–7169, doi: <http://dx.doi.org/10.1073/pnas.0400322101>.
19. Long MA, Deans MR, Paul DL, Connors BW. Rhythmicity without synchrony in the electrically uncoupled inferior olive. *J Neurosci* 2002;22:10898–10905.
20. Martin FC, Handforth A. Carbenoxolone and mefloquine suppress tremor in the harmaline mouse model of essential tremor. *Mov Disord* 2006;21:1641–1649, doi: <http://dx.doi.org/10.1002/mds.20940>.
21. Farrant M, Nusser Z. Variations on an inhibitory theme: phasic and tonic activation of GABA(A) receptors. *Nat Rev Neurosci* 2005;6:215–229, doi: <http://dx.doi.org/10.1038/nrn1625>.
22. Brickley SG, Cull-Candy SG, Farrant M. Development of a tonic form of synaptic inhibition in rat cerebellar granule cells resulting from persistent activation of GABAA receptors. *J Physiol* 1996;497:753–759.
23. Baur R, Minier F, Sigel E. A GABA(A) receptor of defined subunit composition and positioning: concatenation of five subunits. *FEBS Lett* 2006;580:1616–1620, doi: <http://dx.doi.org/10.1016/j.febslet.2006.02.002>.
24. Glykys J, Peng Z, Chandra D, Homanics GE, Houser CR, Mody I. A new naturally occurring GABA(A) receptor subunit partnership with high sensitivity to ethanol. *Nat Neurosci* 2007;10:40–48, doi: <http://dx.doi.org/10.1038/nn1813>.
25. Pirker S, Schwarzer C, Wieselthaler A, Sieghart W, Sperk G. GABA(A) receptors: immunocytochemical distribution of 13 subunits in the adult rat brain. *Neuroscience* 2000;101:815–850, doi: [http://dx.doi.org/10.1016/S0306-4522\(00\)00442-5](http://dx.doi.org/10.1016/S0306-4522(00)00442-5).
26. Hancher HJ, Dodson PD, Olsen RW, Otis TS, Wallner M. Alcohol-induced motor impairment caused by increased extrasynaptic GABA(A) receptor activity. *Nat Neurosci* 2005;8:339–345, doi: <http://dx.doi.org/10.1038/nn1398>.
27. Deng H, Xie WJ, Le WD, Huang MS, Jankovic J. Genetic analysis of the GABRA1 gene in patients with essential tremor. *Neurosci Lett* 2006;401:16–19, doi: <http://dx.doi.org/10.1016/j.neulet.2006.02.066>.
28. Kralic JE, Criswell HE, Osterman JL, et al. Genetic essential tremor in gamma-aminobutyric acidA receptor alpha1 subunit knockout mice. *J Clin Invest* 2005;115:774–779.
29. Schuckit MA, Mazzanti C, Smith TL, et al. Selective genotyping for the role of 5-HT2A, 5-HT2C, and GABA alpha 6 receptors and the serotonin transporter in the level of response to alcohol: a pilot study. *Biol Psychiatry* 1999;45:647–651, doi: [http://dx.doi.org/10.1016/S0006-3223\(98\)00248-0](http://dx.doi.org/10.1016/S0006-3223(98)00248-0).
30. Rajput AH, Robinson CA, Rajput A. Purkinje cell loss is neither pathological basis nor characteristic of essential tremor. *Parkinsonism Relat Disord* 2013;19:490–491, doi: <http://dx.doi.org/10.1016/j.parkreldis.2012.11.019>.
31. Louis ED, Faust PL, Vonsattel JP, et al. Neuropathological changes in essential tremor: 33 cases compared with 21 controls. *Brain* 2007;130:3297–3307, doi: <http://dx.doi.org/10.1093/brain/awm266>.
32. Louis ED, Faust PL, Vonsattel JP, et al. Torpedoes in Parkinson's disease, Alzheimer's disease, essential tremor, and control brains. *Mov Disord* 2009;24:1600–1605, doi: <http://dx.doi.org/10.1002/mds.22567>.
33. Grimaldi G, Manto M. Is essential tremor a Purkinjopathy? The role of the cerebellar cortex in its pathogenesis. *Mov Disord* 2013;28:1759–1761, doi: <http://dx.doi.org/10.1002/mds.25645>.
34. Llinas M, Yarom Y. Specific blockade of the low threshold calcium channel by high molecular weight alcohols. *Soc Neurosci (Abstr)* 1986;12:174.
35. Sinton CM, Krosser BI, Walton KD, Llinás RR. The effectiveness of different isomers of octanol as blockers of harmaline-induced tremor. *Pflugers Arch* 1989;414:31–36, doi: <http://dx.doi.org/10.1007/BF00585623>.
36. Opdyke DL. Fragrance raw materials monographs. Alcohol C-8. *Food Cosmet Toxicol* 1973;11:101., doi: [http://dx.doi.org/10.1016/0015-6264\(73\)90067-9](http://dx.doi.org/10.1016/0015-6264(73)90067-9).
37. Joksovic PM, Choe WJ, Nelson MT, Orestes P, Brimelow BC, Todorovic SM. Mechanisms of inhibition of T-type calcium current in the reticular thalamic neurons by 1-octanol: implication of the protein kinase C pathway. *Mol Pharmacol* 2010;77:87–94, doi: <http://dx.doi.org/10.1124/mol.109.059931>.
38. Nahab FB, Handforth A, Brown T, et al. Octanoic acid suppresses harmaline-induced tremor in mouse model of essential tremor. *Neurotherapeutics* 2012.
39. Bushara KO, Goldstein SR, Grimes GJ, Burstein AH, Hallett M. Pilot trial of 1-octanol in essential tremor. *Neurology* 2004;62:122–124, doi: <http://dx.doi.org/10.1212/01.WNL.0000101722.95137.19>.
40. Shill HA, Bushara KO, Mari Z, Reich M, Hallett M. Open-label dose-escalation study of oral 1-octanol in patients with essential tremor. *Neurology* 2004;62:2320–2322, doi: <http://dx.doi.org/10.1212/WNL.62.12.2320>.
41. Nahab FB, Wittevrongel L, Ippolito D, et al. An open-label, single-dose, crossover study of the pharmacokinetics and metabolism of two oral formulations of 1-octanol in patients with essential tremor. *Neurotherapeutics* 2011;8:753–762, doi: <http://dx.doi.org/10.1007/s13311-011-0045-1>.
42. Haubenberger D, Kalowitz D, Nahab FB, et al. Validation of digital spiral analysis as outcome parameter for clinical trials in essential tremor. *Mov Disord* 2011;26:2073–2080, doi: <http://dx.doi.org/10.1002/mds.23808>.
43. Lavado E, Sanchez-Abarca LI, Tabernero A, Bolanos JP, Medina JM. Oleic acid inhibits gap junction permeability and increases glucose uptake in cultured rat astrocytes. *J Neurochem* 1997;69:721–728, doi: <http://dx.doi.org/10.1046/j.1471-4159.1997.69020721.x>.
44. Bach AC, Babayan VK. Medium-chain triglycerides: An update. *Am J Clin Nutr* 1982;36:950–962.
45. Opdyke DLJ. Monograph—Caprylic acid. *Fd Cosmet Toxicol* 1981;19:237–254, doi: [http://dx.doi.org/10.1016/0015-6264\(81\)90363-1](http://dx.doi.org/10.1016/0015-6264(81)90363-1).
46. Council of Europe (COE). Chemically-defined flavouring substances; heptyl alcohol. Council of Europe Publishing. Strasbourg, France. 2000; p 48.
47. Schwabe AD, Bennett LR, Bowman LP. Octanoic acid absorption and oxidation in humans. *J Appl Physiol* 1964;19:335–337.
48. Oldendorf WH. Carrier-mediated blood-brain barrier transport of short-chain monocarboxylic organic acids. *Am J Physiol* 1973;224:1450–1453.
49. Jenner PM, Hagan EC, Taylor JM, Cook EL, Fitzhugh OG. Food flavourings and compounds of related structure I. Acute oral toxicity. *Food Cosmet Toxicol* 1964;2:327–343, doi: [http://dx.doi.org/10.1016/S0015-6264\(64\)80192-9](http://dx.doi.org/10.1016/S0015-6264(64)80192-9).
50. Traul KA, Driedger A, Ingle DL, Nakhasi D. Review of the toxicologic properties of medium-chain triglycerides. *Food Chem Toxicol* 2000;38:79–98, doi: [http://dx.doi.org/10.1016/S0278-6915\(99\)00106-4](http://dx.doi.org/10.1016/S0278-6915(99)00106-4).
51. Linscher WG, Slone D, Chalmers TC. Effects of octanoic acid on serum-levels of free fatty acids, insulin, and glucose in patients with cirrhosis and in

healthy volunteers. *Lancet* 1967;593–597, doi: [http://dx.doi.org/10.1016/S0140-6736\(67\)90443-6](http://dx.doi.org/10.1016/S0140-6736(67)90443-6).

52. Sills MA, Forsythe WI, Haidukewych D. Role of octanoic and decanoic acids in the control of seizures. *Arch Dis Child* 1986;61:1173–1177, doi: <http://dx.doi.org/10.1136/adc.61.12.1173>.

53. Sills MA, Forsythe WI, Haidukewych D, MacDonald A, Robinson M. The medium chain triglyceride diet and intractable epilepsy. *Arch Dis Child* 1986;61:1168–1172, doi: <http://dx.doi.org/10.1136/adc.61.12.1168>.

54. Carnielli VP, Sulkers EJ, Moretti C, et al. Conversion of octanoic acid into long-chain saturated fatty acids in premature infants fed a formula containing medium-chain triglycerides. *Metab Clin Exp* 1994;43:1287–1292, doi: [http://dx.doi.org/10.1016/0026-0495\(94\)90224-0](http://dx.doi.org/10.1016/0026-0495(94)90224-0).

55. Ashitani J, Matsumoto N, Nakazato M. Effect of octanoic acid-rich formula on plasma ghrelin levels in cachectic patients with chronic respiratory disease. *Nutr J* 2009;8:25.

56. Grosse SD, Khoury MJ, Greene CL, Crider KS, Pollitt RJ. The epidemiology of medium chain acyl-CoA dehydrogenase deficiency: an update. *Genet Med* 2006;8:205–212, doi: <http://dx.doi.org/10.1097/01.gim.0000204472.25153.8d>.

57. Duran M, Mitchell G, de Klerk JB, et al. Octanoic acidemia and octanoylcarnitine excretion with dicarboxylic aciduria due to defective oxidation of medium-chain fatty acids. *J Pediatr* 1985;107:397–404, doi: [http://dx.doi.org/10.1016/S0022-3476\(85\)80514-X](http://dx.doi.org/10.1016/S0022-3476(85)80514-X).

58. Noctor TA, Wainer IW, Hage DS. Allosteric and competitive displacement of drugs from human serum albumin by octanoic acid, as revealed by high-performance liquid affinity chromatography, on a human serum albumin-based stationary phase. *J Chromatogr* 1992;577:305–315, doi: [http://dx.doi.org/10.1016/0378-4347\(92\)80252-L](http://dx.doi.org/10.1016/0378-4347(92)80252-L).

59. Haubenberger D, McCrossin G, Lungu C, et al. Octanoic acid in alcohol-responsive essential tremor: A randomized controlled study. *Neurology* 2013.