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Tremor and Other Hyperkinetic Movements

Reviews

Essential Tremor: What We Can Learn from Current Pharmacotherapy

William Ondo[1*]

[1] Methodist Neurological Institute, Houston, TX, USA

Abstract

Background: The pathophysiology of essential tremor, especially at the cellular level, is poorly understood. Although no drug has been specifically designed to treat essential tremor, several medications improve tremor, and others worsen it. Studying the mechanism of actions of these medications can help our understanding of tremor pathophysiology and contribute to future rational drug design.

Methods: We reviewed literature, concentrating on mechanisms of action, of various medications that mitigate tremor.

Results: Many medications have multiple mechanisms of actions, making simple correlations difficult. Medications that increase the duration of opening of gamma-aminobutyric acid (GABA)-A receptors are most consistently associated with tremor improvement. Interestingly, drugs that increase GABA availability have not been associated with improved tremor. Other mechanisms possibly associated with tremor improvement include antagonism of alpha-2 delta subunits associated with calcium channels, inhibition of carbonic anhydrase, and inhibition of the synaptic vesicle protein 2A. Drugs that block voltage-gaited sodium channels do not affect tremor. The ideal beta-adrenergic blocker requires B2 affinity (non-cardiac selective), has no sympathomimetic properties, does not require membrane stabilization properties, and may benefit from good central nervous system penetration.

Discussion: To date, serendipitous observations have provided most of our understanding of tremor cellular physiology. Based on similarities to currently effective drugs or rational approximations and inferences, several currently available agents should be considered for tremor trials.

Keywords: Tremor, beta-blockers, treatment, gamma-aminobutyric acid, ethanol, primidone

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*To whom correspondence should be addressed. E-mail: wondo@houstonmethodist.org

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Introduction

The pathophysiology of essential tremor (ET) is only partially understood. There is some understanding of culpable macro-circuitry, mostly based on functional positron emission tomography (PET)/single-photon emission computed tomography studies, functional magnetic resonance imaging, tractography, transcranial stimulation, and other electrophysiological techniques.[1] However, there is very little understanding at the cellular level. Post-mortem pathology of ET is inconsistent: variably being normal, demonstrating Lewy body pathology, or cerebellar Purkinje cell degeneration.[2–5] Neurotransmitter studies have been suggestive but not replicated.[6,7]

Our current understanding regarding germane neurotransmitter system pathology in ET is largely inferred from the clinical response of medicines that were serendipitously found to affect tremor. Drugs thought to improve tremor include beta-adrenergic antagonists, primidone, topiramate, ethanol, and benzodiazepines. Less consistent efficacy is reported with many other medications, usually anti-epileptic drugs (AEDs). Medications that worsen tremor also provide physiological clues.

This review will summarize the mechanisms of action of medications that may affect tremor in order to improve our understanding of potential neurotransmitter/receptor pathology and provide a substrate for future rational drug development.

Methods

We initially employed a PubMed search for "tremor". Based on those findings, subsequent PubMed searches included "GABA", "ethanol", primidone", and "levetiracetam". Individual references were also identified from reference sections of identified articles.

Alcohols

Ethanol is arguably the most potent tremor suppressor. Other alcohols such as 1-octanol may also improve tremor, at least in subjects who respond to ethanol.[8,9] However, methylpentynol, a six-carbon chain alcohol, proved clinically ineffective when compared with placebo.[10] Furthermore, 1-octanol is rapidly metabolized to octanoic acid, a carboxylic acid, which is now thought to be the active therapeutic component. Therefore it is not clear whether alcohols improve tremor as a class or whether it is specific to ethanol.

Ethanol improves tremor at relatively low levels, usually within 20 minutes for 3–5 hours, sometimes followed by a rebound tremor augmentation.[11,12] Like other agents, it reduces tremor amplitude but not frequency. Ethanol is arguably the most potent anti-tremor agent, as it proved superior to propranolol and benzodiazepines in small trials.[13,14] Predictors of ethanol response are not identified.[11] Improvement is mostly derived from the central nervous system (CNS), based on weight-loading studies, lack of immediate effect with arteriole infusion, and reduced cerebellar activity on PET following ingestion.[14–16] Ethanol may additionally improve tremor via peripheral mechanisms as it has been shown to reduce enhanced physiologic tremor.[14] It is not known where in the peripheral system this occurs, as it may be a very non-specific relaxing effect, or if it meaningfully contributes to ET suppression.

Ethanol has widespread effects throughout the entire brain and in general is a cellular decoupling agent. Gap junctions are intercellular connections, usually dendro-dendrictic, which allow for direct intercellular cytoplasmic communications. Extensive gap junctions in the inferior olive (IO) are postulated to generate tremor by synchronizing auto-oscillatory firing of IO neurons.[17] These neurons send ascending fibers to cerebellar Purkinje cells. Ethanol has been shown to inhibit gap junction function, potentially associated with opening basolateral calcium-dependent potassium selective channels.[18–20] It is also shown to decrease activity in cerebellar Purkinje cells.[21,22]

A number of specific neurotransmitter systems are also affected by ethanol, most robustly gamma-aminobutyric acid (GABA) systems. GABA-A receptors are ligand-gated ion channels resulting in chloride (Cl^-) influx that hyperpolarizes cells, and therefore inhibits their signaling. The GABA-A receptor is a pentamer, variably employing five of 19 different proteins (alpha-1–6, beta-1–3, gamma-1–3, delta, epsilon, theta, pi, rho-1–3).[23,24] The most common arrangement is two alphas, two betas, and one gamma. Alpha-1 is by far the most common subunit, and is especially present in synaptic receptors. Extra-synaptic GABA-A receptors actually have higher affinity for endogenous GABA, and contain more delta subunits.[25] One new drug is targeting these in early trials for ET (Sage Therapeutics, Cambridge, MA, NCT02277106). For benzodiazepines, affinity to alpha subunits in general is associated with anti-convulsive effects; alpha-1 subunits have been specifically associated with sedation/amnestic effects, and alpha-2 with anxiolytic properties.[26] No data employing tremor models evaluating GABA-A subunits exist. However, there are considerable non-pharmacologic data implicating a role for GABA-A in ET, including cerebrospinal fluid studies that suggest decreased GABA levels.[6,27]

At low doses, consistent with levels that reduce tremor, ethanol potentiates and upregulates GABA-A receptors and probably increases GABA release.[28,29] It has greatest affinity for the GABA-A receptor rich in delta subunits and alpha-4 subunits.[30–33] Anatomically, these are most abundant in the pre-frontal cortex, hippocampus, and cerebellum, suggesting that these may have a specific role in tremor suppression.

Ethanol has many other mechanisms that may affect tremor. It inhibits neurons by specific G-protein-activated inwardly rectifying potassium channels, alters voltage-gated K channels, has multiple effects on *N*-methyl-D-aspartate (NMDA) receptors, and various effects on glycine receptors.[23,34,35] It is not known whether any of these mechanisms mitigate tremor.

Medications that primarily affect GABA systems

AEDs have many different mechanisms of action (MOA), often within the same drug, making the correlation between MOA and tremor reduction difficult (Table 1). For example, topiramate, which improves tremor, has at least five possible MOA that could theoretically affect tremor. Furthermore, only a minority of AED drugs have been studied specifically for tremor in well-designed controlled trials. In general, drugs that potentiate GABA-A receptors (increasing Cl^- influx and hyperpolarizing the cell) such as benzodiazepines and phenobarbital (probably primidone), most consistently improve tremor.

In contrast to ethanol, benzodiazepines have their greatest affinity to GABA-A pentamers with two alpha, two beta, and one gamma subunit, and less to those with delta subunits.[26] Benzodiazepines have a unique binding site distinct from the endogenous GABA site, and increase the frequency of receptor openings, causing Cl^- influx and hyperpolarization. Different benzodiazepines have somewhat different affinities for different pentamer combinations but clinical tremor comparisons among benzodiazepines lack adequate fidelity to correlate these. TPA023, a GABA-A alpha-2, three subtype-selective partial agonist, did show relatively little effect on tremor, at least compared with ethanol.[36] GABA-A receptors containing alpha-4 and alpha-6 units are also insensitive to benzodiazepines.[23]

Barbiturates such as phenobarbital, and probably primidone, increase the duration of receptor opening, as opposed to increasing the frequency of openings, at yet another distinct site on the GABA-A receptor.[37] These appear relatively non-specific for different subunits and will bind to any pentamer with an alpha or beta subunit.[37] Primidone probably acts via this mechanism, although there are remarkably few published data on primidone MOA, because the anti-epileptic effects were historically ascribed to its metabolite, phenobarbital. However, at least one study found primidone superior to phenobarbital against tremor,[38] and primidone improved tremor within an hour of initial ingestion, prior to the formation of any phenobarbital metabolite.[39] Phenylethylmalonamide, the other major metabolite of primidone, has no tremorlytic activity.[40] Therefore, further elucidation of primidone MOA is justified.

Despite the apparent impact of drugs that open GABA-A receptors have on tremor, there is less evidence supporting a role for manipulating endogenous GABA. Endogenous GABA in the CNS is

Table 1. Summary

Drugs Listing in Descending Efficacy for Tremor (+++ to Worsen)[1]	Open GABA Receptors	Increase GABA Synthesis	Inhibit GABA Metabolism Reuptake	Inhibit NA Channel	Inhibit Ca Channels	Inhibit Glutamate Transmission	Carbonic Anhydrase Inhibitor	Other
+++								
Ethanol	+++							
Topiramate	++?	++?	++?	++	++	++ AMPA	+	
Primidone	++?			++				
++								
Benzodiazepines	+++							
Phenobarbital	+++				+	+ AMPA		
+								
Gabapentin		+ GAD?			+++ α2γ			
Pregabalin					+++ α2γ			
Zonisamide				++	++ LVA		+	
Levetiracetam	+	+?	+?	+		+ AMPA		SV2A
Acetazolamide							+++	
TPA023	+++ α2,3							
No effect								
Lamotrigine				+++	++ HVA			
Phenytoin				+++				
Carbamazepine				+++				
Oxcarbazepine				+++				
Lacosamide[1,2]				+++				
Worsen								
Valproate		++		++	++ LVA			
Unknown								
Felbamate	+			++	++	+ NMDA		
Tiagabine[2]			+++ (GAT)					
Vigabatrin			+++GABA-T					

Table 1. Continued

Drugs Listing in Descending Efficacy for Tremor (+++ to Worsen)[1]	Open GABA Receptors	Increase GABA Synthesis	Inhibit GABA Metabolism Reuptake	Inhibit NA Channel	Inhibit Ca Channels	Inhibit Glutamate Transmission	Carbonic Anhydrase Inhibitor	Other
Ethosuximide[1,2]					+++ LVA			
Perampanel						+++ AMPA		
Stiripentol	+++ α3							
Rufinamide[2]				+++				
Retigabine[2] (ezogabine)		+						KCNQ2/3

Abbreviations: α2Δ, Alpha-2 Delta Subunit of Calcium Channel; AMPA, Alpha-Amino-3-Hydroxy-5-Methylisoxazole-4-Propionic Acid; GABA, Gamma-Aminobutyric Acid; GABA-T, GABA Transaminase (GABA metabolism) Vigabatrin; GAD, Glutamate Decarboxylase Activity Increased to Increase GABA; GAT, GABA Transporter-1 (GABA reuptake) Tiagabine; HVA, High-Voltage Activated Calcium Channel Receptor (L, P, N types); KCNQ2/3, Voltage-Gated Potassium Channels, Activating M-current; LVA, Low-Voltage Activated Calcium Channel Receptor (T-type); NMDA, N-Methyl-D-Aspartate; SV2A, Synaptic Vesicle Glycoprotein 2A; +++, consistent controlled trials; ++, inconsistent controlled data and/or consistent positive open label reports; +, any positive report of efficacy without placebo-controlled data, or improved tremor in small trials.

[1] Efficacy based on author's expert opinion.

[2] Tremor listed as adverse event in ≥ 10% suggesting a lack of effect.

converted from glutamate by L-glutamic acid decarboxylase using pyridoxal phosphate (the active form of vitamin B6) as a cofactor. Drugs that increase GABA availability (tiagabine, vigabatrin, valproate) have not been associated with tremor improvement, and may even exacerbate tremor in some cases.[41,42] Tiagabine, which increases GABA levels by blocking the synaptic GABA transporter (GAT-1), has been reported to worsen tremor. This protein is mostly found in the hippocampus and neocortex. Vigabatrin, which prevents GABA degradation via irreversible inhibition of the mitochondrial enzyme GABA transaminase, has not demonstrated tremor benefit, and is reported to cause tremor as an adverse effect.[43] Valproate, which increases GABA turnover and synthesis, along with several other MOA, often worsens tremor. Topiramate, which does improve tremor, may increase GABA-A receptor density, although other potential tremorlytic mechanisms also exist. Felbamate (tremor response unknown) also increases receptor density but has not been evaluated for tremor and is seldom used. The GABA-A agonist progabide failed to improve tremor,[44,45] although the GABA-A agonist muscimol improved tremor when injected directly into the ventral intermediate nucleus in six subjects undergoing deep brain stimulation.[46]

Sodium oxybate (γ-hydroxybutyrate, GHB) is a very powerful cellular decoupler that may improve tremor, at least in those who are also responsive to ethanol.[47] GHB modulates GABA-B receptors, and inhibits glutamate transmission via stimulation of a relatively novel GHB receptor.[48] It also inhibits dopamine release, but after a short time (T1/2 90–120 minutes) there is a rebound increase in dopamine release.

The GABA-B receptor is a metabotropic G-protein-coupled receptor protein. Baclofen, a GABA-B agonist, is not thought to improve ET, although a single case reported improved cerebellar outflow tremor with intrathecal baclofen.[49] No other GABA-B agonist is known to improve tremor; therefore, the mechanism by which GHB may improve tremor, and whether GABA-B mechanisms are involved, is not known.

Other receptor systems that may be implicated in tremor

Carbonic anhydrase inhibitors, including acetazolamide and methazolamide, and to a lesser extent topiramate and zonisamide, may improve tremor, although data supporting the more potent and specific carbonic anhydrase inhibitors are modest.[50–53] These drugs locally acidify brain areas and increase bicarbonate ion concentrations. pH buffering of extra- and intracellular spaces is mainly carried out by the $CO_{(2)}/HCO_{(3)}^{(-)}$ buffer, which is regulated by the zinc enzyme carbonic anhydrase. Acidification facilitates GABA-A receptor potentiation and reduced NMDA receptor activity. This mechanism may facilitate the effect of carbonic anhydrase inhibitors on tremor and seizure, although this is speculative. The effects of pH on tremor have never been carefully studied, although hyperventilation, which increases pH, anecdotally can worsen tremor.

Agonist at the alpha-2 delta subunit of Ca^{2+} channels (gabapentin and pregabalin) may improve tremor.[54–58] These drugs bind to the

alpha-2 delta subunit of a variety of different Ca^{2+} channel subtypes and are most densely found in the spinal cord and thalamus. Stimulation of alpha-2 delta subunits inhibits the subsequent transmission of other neurotransmitters, usually glutamate, and they are thus usually inhibitory. The mechanism is quite distinct from "calcium channel blockers".

Levetiracetam may improve tremor.[59,60] It is proposed to have a unique MOA, inhibition of the synaptic vesicle protein 2A (SV2A).[61] The role of this protein is poorly understood but, within the brain, is located primarily in the cortex, hippocampus, and cerebellum. Interestingly, botulinum toxin A also affects entry into neurons by binding to this receptor protein. Other inhibitors of SV2A are being developed for seizures but none has been tested against tremor.

Receptor systems with questionable or no involvement based on clinical data

Glutamate is the most common excitatory neurotransmitter, and has wide brain distribution. The main receptors for glutamate are kainate, NMDA, and alpha-aminon-3-hydroxy-5-methylisoxazole-4-proprionic acid (AMPA). Topiramate, which improves tremor, partially inhibits kainate receptors and possibly alters AMPA affinities, but also has other possible MOA. Levetiracetam and phenobarbital also have very mild effects on AMPA receptors. Perampanel, a relatively new AED, markedly and specifically inhibits AMPA receptors but has not been tested in tremor. Drugs that modulate NMDA receptors (amantadine, memantine, dextromethorphan, riluzole) are not known to improve tremor.[62,63] Overall, there is no compelling direct evidence supporting a role for glutaminergic modulation except that alpha-2 delta Ca^{2+} blockers, which inhibit release of glutamate, may improve tremor modestly. An exploratory study of the AMPA antagonist perampanel may be justified as no other drug so robustly affects AMPA receptors.

Many AED medications, some of which may improve tremor, have some affinity for various calcium channels, making this group particularly difficult to analyze. T-type-specific Ca^{2+} blockers, including zonisamide, improve tremor in animal models and possibly in humans.[64,65] Interestingly, there are more robust clinical data supporting zonisamide for parkinsonian rest tremor and there is an expanding interest in T-type Ca^{2+} receptors as an intrinsic oscillator, and target for Parkinson disease therapy. Ethosuxamide is an old, more specific T-type inhibitor but its effect on tremor is not known.

Inhibition of N- and P/Q-type calcium channels is less implicated in tremor although phenobarbital, topiramate, and levetiracetam modestly inhibit these. Non-specific calcium channel blockers, especially those with good CNS penetration (nicardipine and nifedipine), are noted to exacerbate tremor in humans and animal models of tremor.[66] It is not known whether this represents a direct chemical effect or is due to a compensatory release of catecholamines to compensate for reduced blood pressure.

Several AED medications (phenytoin, carbamazepine, lamotrigine, lacosamide) primarily inhibit voltage-gated sodium (Na^{+}) channels. These receptors are widely distributed and primarily responsible for action potentials. However, this drug class does not appear to improve nor worsen tremor.[67]

The novel potassium (KCNQ2/KCNQ3 subunit) channel antagonist retigabine has never been studied in tremor. Tremor is listed as an adverse event in seizure studies.

There is no known monoaminergic (norepinephrine, dopamine, histamine, serotonin) drug that benefits tremor. Serotonin re-uptake inhibitors often cause or worsen tremor. Norepinephrine analogues may worsen tremor, especially at high doses. Dopamine agonists, antagonists, and depletes have little effect on action tremor. Histamine-3 inverse agonists are a new class of medications being studied for a variety of neurological conditions including attention deficit, fatigue, and excessive daytime sleepiness. The histamine-3 inverse agonist MK-0249 did not show benefit in a single dose study in ethanol-responsive ET patients.[68] Histamine type 1 or 2 antagonists are not thought to affect action tremor.

Beta-blockers

Beta-adrenergic blocker reduces hand tremor in 50–70% of subjects in a dose-dependent manner. Most studies comparing propranolol to other beta-blockers have shown that subjects usually respond to both or neither study drugs, suggesting a class effect. However, comparing efficacy of different beta-blockers can provide some evidence regarding ideal MOA.

Although ET probably originates in the CNS, beta-blockers appear to at least partially attenuate tremor via a peripheral site. Water-soluble beta-blockers, such as sotalol, arotinolol, and LI32-468, penetrate the CNS poorly but improve tremor equally to propranolol.[67,69] Intra-arterial propranolol attenuates isoproterenol-induced enhanced physiologic tremor within seconds, whereas maximal clinical tremor suppression takes up to 2 hours for ET. The longer effect latency to ET tremor suppression suggests a site of action with relatively isolated bioavailability, such as the CNS. However, this apparent anomaly can be explained by the presence of a blood–tissue barrier that surrounds extrafusal muscle spindles, a proposed peripheral site of action for beta-blockers. Alternatively, CNS beta-2 blockade may help diminish tremor by reducing CNS norepinephrine release or other mechanisms. One recent study found beta-blocker-responsive ET subjects had a greater reduction in CNS glucose metabolism compared with non-responsive subjects.[70] Since all beta-blockers enter the CNS to some degree, contribution from a CNS site of action cannot be entirely eliminated.

"Non-cardioselective" beta-2 blockade appears necessary for maximal tremor suppression (Table 2). Trials with atenolol and metoprolol, agents with relative beta-1 selectivity, suggest that the drugs are mildly inferior to propranolol, although they are usually still better than controls.[67] Several studies have demonstrated efficacy of metoprolol; however, these employed doses at which beta-1 selectivity is lost.[71,72] The beta-2-selective agents LI32-468 and ICI 188-551 have demonstrated equal potency to propranolol.[73] Beta-2 agonists (asthma inhalers) are also most associated with causing tremor and beta-2 receptors are most abundant in muscle and peripheral nerve. Agents

Table 2. Summary of Beta Blockers

	Typical Dose Daily mg/frequency	Lipid Solubility	Sympathetic Activity	Beta-1 Activity	Beta-2 Activity	Tremor Efficacy
Propranolol	40–320/bid	+++	–	+	+	+++
Arotinolol	10–40/bid?	+	–	+	+	+++
Nadolol	80–240/qd	+++	–	+	+	+++
Sotalol	80–320/bid	+	–	+	+	+++
Timolol	10–20/bid	++	±	+	+	++
Metoprolol	100–200/bid	++	–	+	±	++
Atenolol	50–100/qd	+	–	+	±	+
Pindolol	10–30/bid	++	+	+	+	–

Potency ratios: arotinolol ≥ timolol > propranolol ≥ metoprolol > atenolol > nadolol (doses where metoprolol loses B1 selectivity); propranolol > atenolol; propranolol >> pindolol.

with partial sympathomimetic properties (mixed agonist/antagonist) such as pindolol and practolol have not shown any tremorlytic efficacy and may actually exacerbate underlying ET or physiologic tremor.[74]

Membrane stabilization properties found in some beta-blockers block action potentials by inhibiting the Na^+ channel, but this property appears unrelated to their tremorlytic effect. Buferolol, sotalol, and LI32-468 lack membrane-stabilizing properties yet are potent tremorlytic agents. Conversely, D-isomer propranolol (an equally potent stabilizer to L-isomer propranolol) lacks any tremorlytic properties.

In summary, the ideal beta-blocker lacks sympathomimetic properties, possesses beta-2 antagonist activity, and does not necessarily require good CNS penetration. To date, no agent is theoretically or empirically superior to propranolol, with the possible exception of arotinolol. Nadolol or sotalol may offer equal efficacy with less CNS sedation. It is likely that these agents mitigate tremor at the peripheral nerve and/or muscle more than at the presumed CNS origin of ET.

Considering animal models of tremor

Several animal models of tremor have been developed including isoproterenol (beta-agonist), the GABA-A receptor alpha-1 knock-out mouse,[75] and most commonly the harmaline model.[76,77] Injected harmaline increases inferior olivary nuclei synchrony and clinical tremor.[78] Many medications and mechanisms that improve human tremor also improve harmaline tremor (ethanol, benzodiazepines, primidone, and other GABA-A antagonists; GHB, and beta-blockers, although not consistently). Some mechanisms where the human clinical repose is less established (NMDA antagonists, AMPA inhibitors, T-type calcium channel antagonists, cannabidiol agonists, gap junction blockers) also improve harmaline-induced tremor.[64,78,79] However, some drugs that have no clear effect, or even worsen human tremor, also improve harmaline models (dopamine agonists, GABA-B agonists, carbamazepine, lithium, and valproate). Therefore, although very useful, this models lacks excellent correlation with human outcomes.[77]

Future directions

Based on similarities to currently effective drugs or rational approximations and inferences, several available agents should be considered for tremor trials. Ethosuxamide is an old, potent Ca^{2+} T-type blocker, which could be more potent than zonisamide for tremor of ET and Parkinson disease, if this mechanism is relevant. Perampanel is a novel AED that specifically and robustly inhibits AMPA receptors and does not seem to worsen tremor in epilepsy trials. Clobazam is a novel long acting 1,5-benzodiazepine with somewhat unique GABA affinities and relatively little sedation. Stiripentol is an AED, approved in many countries for Dravet's syndrome, which increases the duration of opening of the GABA-A receptor, similar to barbiturates. It may also prevent metabolism of endogenous GABA. Several different and not widely available beta-blockers can also be considered, especially arotinolol. The beta-2-selective drugs LI32-468 and ICI 188-551 should also be reconsidered, as they may be better tolerated than current non-selective agents.

Conclusion

Our lack of understanding of ET pathophysiology has prevented the rational development of effective agents. No drug initially developed for tremor exists, although drugs with multiple MOA improve tremor inconsistently. Potentiating GABA receptors in the CNS and inhibiting beta-adrenergic systems most consistently improve tremor. Inhibiting glutaminergic systems, carbonic anhydrase, SV2A receptors, and alpha-2 delta subunits less consistently improve tremor, whereas Na channel inhibition does not affect tremor. Until a better understanding exists, we will rely on clues from existing medicines to design treatments for ET.

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