

Essential Tremor: Clinical 2 Working Group Session 2 Document

What Can We Learn from Available Therapies and What Do We Need to Implement Clinical Trials and Advance Clinical Research in ET

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Tremor: What We Know From Current Treatments

Medicines thought to improve tremor include Beta adrenergic antagonists, primidone, topiramate, ethanol, and benzodiazepines. Less robust efficacy is reported with many other medications, usually anti-epileptic drugs (AED).

Alcohols

Ethanol improves tremor at relatively low levels, usually within 20 minutes for 3-5 hours, sometimes followed by a rebound tremor augmentation. Other alcohols such as 1-octanol and sodium oxybate may also improve tremor. However, methylpentynol, a six carbon chain alcohol proved clinically ineffective when compared to placebo. Improvement with ethanol is likely central based on weight loading studies and reduced cerebellar activity on PET, although it can also lessen physiological tremor. Ethanol has diffuse decoupling effects on the brain, has extremely widespread CNS actions, but especially increases activity (chloride influx) at GABA-A receptors. At low doses, consistent with dosing that reduces tremor, it has greatest affinity to GABA-A receptor rich in delta sub-units, most abundant in the pre-frontal cortex, hippocampus and cerebellum. Ethanol also specifically inhibits neurons by specific G-protein-activated inwardly rectifying potassium (GIRK) channels, alteration in NMDA receptors and various effects on glycine receptors.

Anti-Epileptic Medications (AED)

AED medications have many different MOA, often within the same drug, making correlation of mechanism of action (MOA) and tremor reduction difficult. Topiramate, which improves tremor, is particularly difficult since it has many MOA. In general, drugs that potentiate GABA-A receptors (increasing Cl influx and depolarizing the cell) such as benzodiazepines and phenobarbital (possibly primidone), tend to most improve tremor. Interestingly drugs that increase GABA availability (tiagabine, vigabatrin) have not been associated with tremor improvement, and possibly cause exacerbation. Carbonic anhydrase inhibitors may modestly improve tremor. These drugs locally acidify brain areas resulting in GABA-A potentiation and NMDA dampening. Agonist at the α -2 delta subunit of Ca channels

inhibit synaptic transmission of other neurotransmitters, usually glutamate, are present in many different Ca channel subtypes, and may improve tremor. Direct inhibitors of calcium channels (N, T, L), sodium channels, potassium channels (retigabine) and glutamate inhibitors do not appear to overtly reduce tremor.

B-Blockers

Beta-adrenergic blocker reduce 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. Comparing efficacy of different B-blockers provide evidence regarding mechanism of action.

Although ET probably originates in the CNS, beta-blockers appear to attenuate tremor predominately via a peripheral site. Water soluble beta-blockers, such as sotalol, arotinolol and LI 32-468 penetrate the CNS poorly but improve tremor equally to propranolol. Maximal clinical tremor suppression occurs within two hours for ET but intra-arterial propranolol attenuates isoproterenol induced enhanced physiologic tremor within seconds. The longer effect latency to ET tremor suppression still suggests a site of action with relatively isolated bioavailability, such as the CNS. This apparent anomaly, however, can be explained by the discovery of a blood-tissue barrier surrounding 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 mechanism. Since all beta-blockers enter the CNS to some degree, contribution from a CNS site of action cannot be entirely eliminated.

Beta-2 blockade (non-cardioselective) appears necessary for maximal tremor suppression. Trials with atenolol and metoprolol, agents with relative beta-1 selectivity, suggest that the drugs are inferior to propranolol. Several studies have demonstrated metoprolol's efficacy, however these tended to employ doses at which beta-1 selectivity is lost. The beta-2 selective agents LI32-468 and ICI 188-551 have demonstrated equal potency to propranolol. Beta-2 agonists (asthma inhalers) are also most associated with causing tremor. Agents with partial sympathomimetic properties (mixed agonist/antagonist) such as pindolol and practolol have not shown any tremorolytic efficacy and may actually exacerbate underlying ET or physiologic tremor.

The membrane stabilization properties, which block action potentials via inhibiting Na channel, of beta-blockers appears unrelated to their tremorolytic effect. Buferolol, sotalol and LI 32-468 lack membrane stabilizing properties yet are potent tremorolytic agents. Conversely D-isomer propranolol (an equally potent stabilizer to L-isomer propranolol) lacks any tremorolytic properties.

In summary, the ideal beta-blocker lacks sympathomimetic properties, possesses beta-2 antagonist activity, and does not necessarily require good CNS penetration. No agent to date is theoretically or empirically superior to propranolol. Nadolol or sotalol may offer equal efficacy with less CNS sedation.

	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		Synaptic vesicle protein
acetazolamide							+++	
TPA023	+++ α 2,3							
NIL								
lamotrigine				+++	++ HVA			
phenytoin				+++				
carbamazepine				+++				
oxcarbazepine				+++				
Lacosamide#*				+++				
WORSEN								
valproate		++		++	++ LVA			
UNKNOWN								
Felbamate	+			++	++	+NMDA		
Tiagabine*			+++ (GAT)					
Vigabatrin			+++GABA-T					
Ethosuximide#*					+++ LVA			
Perampanel						+++ AMPA		
Stiripentol	+++α-3							
Rufinamide*				+++				
Retigabine* (ezogabine)		+						KCNQ2/3

* Tremor listed as AE in >10% or reported to worsen tremor in small trials, # Improved harmaline model but open label human study negative

GAD Glutamate decarboxylase activity increased to increase GABA, SV2A Synaptic Vesicle glycoprotein, GAT GABA transporter-1 (GABA reuptake) tiagabine, GABA-TGABA-transaminase (GABA metabolism) vigabatrin, AMPA alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid, NMDA N-methyl-D-aspartate, α2γ alpha-2 delta sub-unit of calcium channel blocker, KCNQ2/3voltage-gated potassium channels, activating M-current

	Typical Dose daily mg/freq	Lipid Solubility	Sympathetic Activity	beta-1 activity	beta-2 activity	Tremor efficacy
propranolol	40-320/BID	+++	--	+	+	+++
nadolol	80-240/qD	+++	--	+	+	+++
sotolol	80-320/BID	+	--	+	+	+++
timolol	10-20/BID	++	+/-	+	+	++
metoprolol	100-200/BID	++	--	+	+/-	++
atenolol	50-100/qD	+	--	+	+/-	+
pindolol	10-30/BID	++	+	+	+	--

propranolol ≤ arotinolol

propranolol ≥ metoprolol (doses where metoprolol loses B1 selectivity)

propranolol > atenolol

propranolol >> pindolol