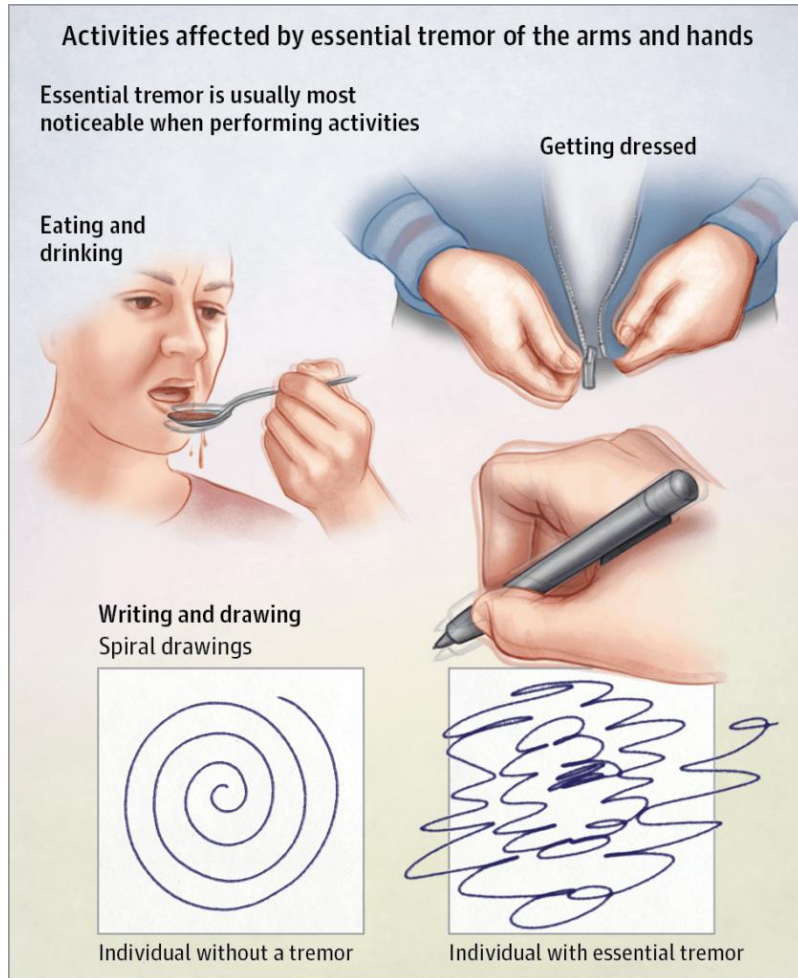


LPCN 2203
Oral NAS for Essential Tremor

Essential Tremor (ET)

No new drug approved in 50+ years



- Tremor highly disabling and stigmatizing
- Stress can aggravate tremor in social setting
- Major impact on activities of daily living leading to unemployment, anxiety and depression¹
- Most common impacts on activities of daily living are pouring liquids and writing/typing (100%) and grooming/hygiene, drinking, dressing, eating, and reading (80-85%)
- 90% of participants indicated the emotional impact of ET
- 75% reported tremor-related worry or anxiety
- Majority of patients require caregiving¹

ET Patient Journey and Commonly used medications

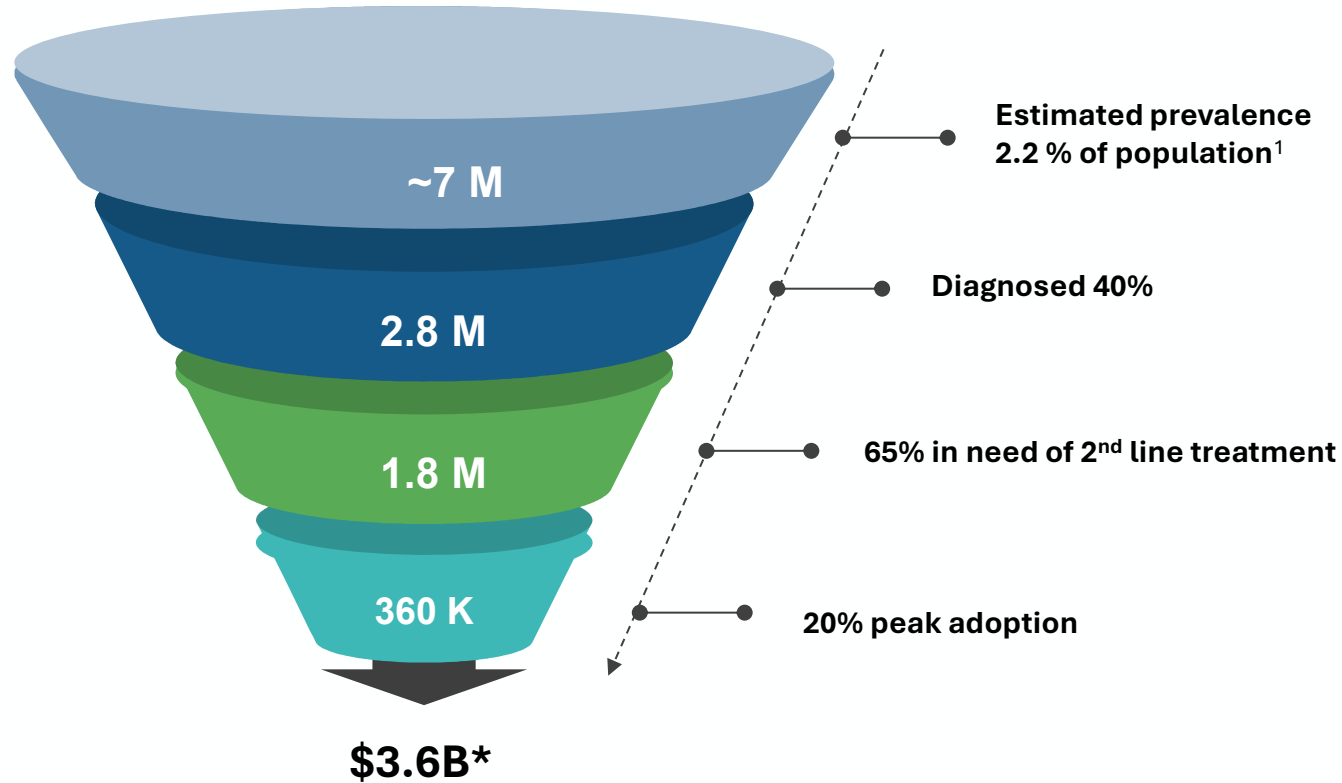
- First line treatment of propranolol frequently started at PCP
- 2nd and 3rd line treatments (e.g., primidone, benzodiazepine, gabapentin, topiramate) at general neurologist and movement disorder clinics
- Patient survey indicates on-going management by PCP (26%), general neurologist (23%), movement disorder specialist (19%)

ESSENTIAL TREMOR: COMMONLY USED MEDICATIONS

DRUG	PROPRANOLOL	PRIMIDONE	GABAPENTIN	ALPRAZOLAM	TOPIRAMATE	NIMODIPINE	ZONIZAMIDE
Brand	Inderal ®	Mysoline ®	Neurontin ®	Xanax ®	Topamax ®	Nimotop ®	Zonegran
Use in ET I	1 st line	1 st line	2 nd line	2 nd line	2 nd line	3 rd line	3 rd line
Class	beta-blocker	anti-convulsant	AED	anti-anxiety	AED	vasodilator	AED
MoA	beta blocker	barbiturate	GABA analog	benzodiazepine	complex	L-type Ca ²⁺ chan.	CA inhibitor
daily dosing / frequency	80-160 mg BID	50-250 mg every bedtime	100-300 mg TID	up to 3mg TID	150-300 mg BID	120 mg QID	
Evidence-level	Level A; FDA approved	Level A	Level B	Level B	Level B	Level C	Insuff. Evidence
Response rate	~40-60%	~30-50%	30%	75%	30-40%	50%	50%
Tremor Reduction	50%	50-70%	30-40%	50%	20-37%	50%	25%
dropout rate	20-35%	20-30%	10%	<10%	30%	unknown	unknown
Side Effects	44.90% AE dizziness, fatigue	72% AE flu like symptoms significant sedation	"Generally well tolerated" sedation, dizziness, ataxia, weight gain in 30-40% pts	sedation, cognitive impairment,	concentration difficulties, somnolence, fatigue	hypotension, edema, headaches in 10-20% pts	trouble concentrating, body aches, flu symptoms, sore mouth; back pain
Alcohol DDI	Moderate	Major	can increase side effects	increased effects of EtOH	moderate, can increase side effects	moderate additive effect	can increase side effects
Number of major DDI	68	232	7	138	360	53	361

Essential Tremor (ET)

Market potential - \$3B+ blockbuster opportunity as 2nd line with 20% peak adoption



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1. Louis ED, Ottman R. Tremor Other Hyperkinet Mov (N Y). 2014;4:259

2. Gerbasi et al. Patient experiences in essential tremor: Mapping functional impacts to existing measures using qualitative research. MDS 2023.

*indicative pricing ~ \$10K/patient/year

Essential Tremor Management – No New Drugs Approved In 50+ Years

Daytime efficacy and improved tolerability remain an unmet need



Unmet Need

Superior benefit to risk profile

- Improve efficacy
- Fewer side effects
 - Somnolence
 - Dizziness
 - Constipation
- Address anxiety/depression comorbidity
- Disease-modifying effects



Standard of Care Limitations

Unfavorable benefit to risk profile³

- Most patients are intolerant or have an inadequate response to first line propranolol or primidone
- 33% experienced no benefit from propranolol and 35% discontinued due to side effects
- 17% reported no benefit from primidone and 23% discontinued due to side effects



Competitive Landscape

- Propranolol is the first line therapy
- 65% in need of second line treatment
- ~44% of diagnosed patients treated with propranolol or primidone²
- Ulixacaltamide: Positive P3 results⁴
 - Discontinuation rate 36-38%
 - TEAEs ≥ 10%: Constipation (25-29%), dizziness (24-26%), brain fog (12-19%), paraesthesia (10-12%), fatigue (9-10%), insomnia (8-12%), and headache (8-13%)

LPCN Product Target Differentiation



Novel MOA



Favorable benefit to risk profile



Daytime efficacy



Endogenous NAS



Potential to address anxiety and depression comorbidities



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