Safety of Non-Invasive Median & Radial Nerve Stimulation

The concept of transcutaneous electrical stimulation of underlying nerves to treat chronic conditions has a rich history stemming back as far as 63 A.D., which matured with the advent of electrostatic devices in the 16th century. The first wearable transcutaneous electrical nerve stimulation (TENS) device emerged in 1974 to treat chronic pain, to the credit of American neurosurgeon Clyde Norman Shealy MD, PhD.[35] Since then, there have been many studies investigating the safety and efficacy of transcutaneous electrical nerve stimulation to treat a myriad of chronic disorders. Based off of these studies, TENS devices and other transcutaneous nerve stimulation devices have a demonstrated low significant adverse event rate and risk profile, regardless of stimulation location on the body *(Table 1)*.

Stimulation Location	Indication	Study Duration	Adverse Events	Reported Event Rate Percent (%)(subjects/ study population)	References
Stimulation Region: Head & Neck					
Neck *(cervical vagus nerve)*	Epilepsy	9 months	Hoarseness, headache, constipation	**30%** (3/10)	Stefan et al., 2012
	Cluster headache	1 month	Lip pull, skin irritation, metallic taste	**26%** (13/50)	Goadsby et al., 2018
	Cluster headache	3 months	Application site reaction (burning, tingling, skin irritation, etc.), lip pull, metallic taste	**14%** (18/128)	Silberstein et al., 2016
Ear *(auricular vagus nerve)*	Migraine	3 months	Mild or moderate pain, paresthesia, or pruits during or after stimulation, and erythema, ulcer or scab	**59%** (27/46)	Straube et al., 2015
	Migraine	3 months	Application site reaction, nasopharyngitis, erythema pain, discomfort	**18%** (21/120)	Tassorelli et al., 2018
Face *(trigeminal nerve)*	Depression	2 months	Skin erythema and headache	**20%** (2/11)	Cook et al., 2013
Stimulation Region: Upper Body					
Hand *(median, radial, ulnar nerves)*	Carpal tunnel syndrome	1 month	n/a	**0%** (0/11)	Naeser et al., 2002
Back *(spinal cord)*	Diabetic neuropathy	1 month	Burning sensation	**6%** (1/18)	Kumar et al., 1997
	Paralysis	1 month	n/a	**0%** (0/6)	Gad et al., 2018
Stimulation Region: Lower Body					
Lower Leg *(tibial cord)*	Incontinence	3 months	Discomfort due to stimulation	**2%** (1/53)	Leroi et al., 2012
Knee *(tibial, saphenous nerves)*	Osteoarthritis	3 months	Transient rash	**18%** (7/39)	Garland et al., 2007

Table 1 *Reported device related adverse events with non-invasive electrical stimulation methods to treat a variety of disorders.*[1-11]

The Cala Trio™ device is a medical device that was designed for the delivery of transcutaneous electrical stimulation of the median and radial nerves in the wrist. This device is the first of its kind, with several studies that have demonstrated the clinical effectiveness of nerve stimulation devices to treat symptomatic hand tremor in patients with essential tremor (ET). To date, reported significant adverse events or unanticipated adverse device effects have not been observed in any of the clinical studies investigating the safety and efficacy of the Cala Trio™ or previous generation Cala devices.

In the first acute multicenter trial, the adverse event rate was low at 3% (3/93 subjects) and observed adverse events included significant and persistent skin irritation (including redness, itchiness, and/or swelling) in two subjects who received treatment and sensation of weakness or stinging pain in the wrist *(Table 2)*. All adverse events were mild and resolved within 24 hours without treatment or sequelae.[34]

Therapy	Adverse Event	Reported event rate (percent(%) subjects/study population)	References
Pharmacotherapy			
Beta-blockers	Bradycardia	**3%** (6/175) Arotinolol; **4%** (1/25) and **6%** (10/175) Propranolol	Lee et al., 2003; Koller et al., 1989
	Headache	**13%** (2/16) and **3%** (6/175) Propranolol; **0.5%** (1/175) Arotinolol	Lee et al., 2003; Calzetti et al., 1982
	Hypotension	**57%** (43/75) Propranolol; **15%** (11/76) Clonidine	Serrano-Duenas et al., 2003
	Fatigue	**31%** (5/16) Propranolol; **19%** (3/16) Metoprolol	Calzetti et al., 1982
Antiepileptics	Serious adverse events	**4%** (5/117) Topiramate	Ondo et al., 2006
	Dizziness	**8%** (2/25) Gabapentin; **11%** (13/117) Topiramate; **22%** (4/18) Gabapentin; **27%** (3/11) Primidone; **11%** (3/27) **20%** (4/20) Pregabalin	Ondo et al., 2000, 2006; Pahwa et al., 1998; Sasso et al., 1990; Zesiewicz et al., 2013; Ferrara et al. 1990
	Sedation	**32%** (6/19) **73%** (8/11) Primidone	Gunal et al., 2000; Sasso et al., 1990
Anxiolytics & Antipsuchotics	Constipation	**17%** (2/12) **73%** Alprazolam	Huber et al., 1988
	Sedation or drowsiness	**50%** (6/12) Alprazolam; **87%** (13/15) Clozapine	Huber et al., 1988; Ceravolo et al., 1999
Botulinum Toxin	Hand weakness	**30%** (13/43) Low dose; **70%** (31/45) High dose	Brin et al., 2001
	Pain at injection site	**5%** (2/43) Low dose; **2%** (1/45) High dose	Brin et al., 2001
Invasive Therapies			
DBS	Death	**17%** (8/46)	Borretzen et al., 2014
	Dysarthria	**57%** (4/7); **65%** (17/26)	Baalzabal-Carvallo et al., 2013; Borretzen et al., 2014
	Lead breakage/failures	**32%** (6/19)	Blomstedt et al., 2007
Thalamotomy	Dysarthria	**14%** (3/21)	Zirh et al., 1999
	Weakness	**8%** (3/37)	Akbostanci et al., 1999
MRI-guided focused ultrasound	Gait ataxia/disturbances	**28%** (5/18)	Zaaroor et al., 2018
	Paresthesia or numbness	**38%** (21/56)	Elias et al., 2016
	Pin-site pain, edema or bruising	**30%** (17/56)	Elias et al., 2016
	Taste disturbance	**5%** (3/56); **22%** (4/18)	Elias et al., 2016; Zaaroor et al., 2018
Stereotactic Radiosurgery	Death	**19%** (31/161)	Young et al., 2010
	Hemiparesis	**3%** (4/161)	Young et al., 2010
	Sensory loss	**3%** (5/161)	Young et al., 2010
Noninvasive Non-Pharmacotherapy Options			
Cala Trio ™	Skin irritation, sensation of weakness, or stinging in the wrist	3% (3/93)	Pahwa et al., 2019

Table 2 *Common treatment options for essential tremor and published adverse events and occurrence rates for each adverse event.*[12-34]

In the subsequent month-long study, there was an observed 11% (7/62) device-related (definite or possibly) adverse event rate. Observed events included significant and persistent skin irritation (1/62), significant discomfort (1/62), persistent pain from stimulation (1/62), wrist soreness from Velcro (1/62), pinky muscle contraction (1/62), electric shock sensation while using device (1/62), and a pulling/prickling sensation on the forehead (1/62). All adverse events resolved without sequelae and required only minimal intervention such as review of product labeling or reduction of stimulation amplitude.

The observed therapeutic response from median and radial nerve stimulation is achieved without the risks of surgical or pharmacological intervention, such as the risk of hemorrhage (5% reported rate) or infection (4% reported rate) with DBS implantation or other invasive procedures, or side effects from ET medications *(Table 1)*. One of the more recent invasive FDA approved therapies to treat hand tremor in ET patients is focused ultrasound thalamotomy. While focused ultrasound thalamotomy is demonstrated to significantly reduce hand tremor (47% reduction after 3 months), Elias et al. reported the adverse event of 56 subjects who received thalamotomy; these adverse events included gait disturbance in 36% of patients and paresthesia or numbness in 38% of patients.[32]

Finally, additional TENS studies investigating the underlying physiological changes with transcutaneous electrical stimulation at the wrist in particular support the safety of chronic peripheral stimulation of the median and radial nerves at the level of the wrist. Two of these studies tested nerve integrity using motor and sensory nerve conduction tests on the median nerve, and showed that there was no significant change in motor or sensory nerve performance or conduction following stimulation.[19, 37, 38] Taken together, these studies suggest that median and radial nerve stimulation has a low side effect profile as compared to current available therapies to treat hand tremor symptoms in ET.

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