



# Neurostimulation for Restless Legs Syndrome

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# Disclosure Information

Type of Affiliation

Commercial Entity

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# Current treatment approaches for RLS

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## Modify reversible causes

- Iron Deficiency (keep Ferritin > 50)
- Medication-Induced (SRIs, DA antagonists, antihistamines)

## Pharmacologic approaches

- Dopaminergic agonists (pramipexole, ropinirole, rotigotine patch)
- Alpha 2 delta ligands (gabapentin, pregabalin)
- Opioids (oxycodone, methadone)
- Iron (oral, intravenous)



# Limitations of existing treatments

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## Dopamine agonists

- Augmentation
- Loss of efficacy
- Acute side effects: nausea, sleepiness

## Alpha 2 delta ligands

- Sedation, dizziness, weight gain

## Opioids

- Risk of abuse; respiratory suppression, constipation



# Why would neurostimulation be effective for RLS?

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## Symptomatic reasons

- By definition, movement (a form of neurostimulation) is effective
- “Counterstimulation” both before and after provides relief of both pain and itch
- True as well for RLS symptoms for some people: massage, hitting legs, hot water, exercise



# Why would neurostimulation be effective for RLS?

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## Pathophysiology

- Hyperexcitability of CNS, most notably at spinal cord
- Vascular theories of low oxygen in the lower extremity muscles, and that movement increases oxygen supply

Review Article

# Sensory symptoms in restless legs syndrome: the enigma of pain

John W. Winkelman<sup>a,\*</sup>, Alison Gagnon<sup>b</sup>, Andrew G. Clair<sup>c</sup>

RLS has many similar features to both pain and itch, with peripheral and central nervous system involvement, a premonitory sensation and need to move, as well as a strong emotional component.

# Transcutaneous electrical nerve stimulation (TENS) has been used widely in physical therapy



TENS is the application of a mild electrical current to the skin nerve fibers using surface electrodes. The amplitude of the current is usually adjusted to just above or just below the sensory threshold



# EFFICACY OF TRANSCUTANEOUS ELECTRIC NERVE STIMULATION IN THE TREATMENT OF PAIN IN NEUROLOGIC DISORDERS

## CHRONIC LOW-BACK PAIN

What is the efficacy of TENS in the treatment of chronic low-back pain?

**Strong evidence**

TENS is not recommended for the treatment of chronic low-back pain due to lack of proven efficacy (**Level A<sup>+</sup>**, two Class I studies).

## PAINFUL DIABETIC NEUROPATHY

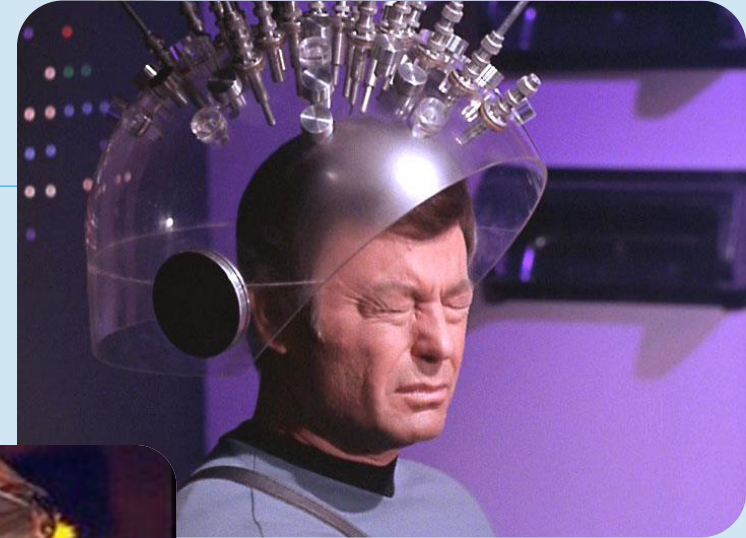
What is the efficacy of TENS in the treatment of painful diabetic neuropathy?

**Good evidence**

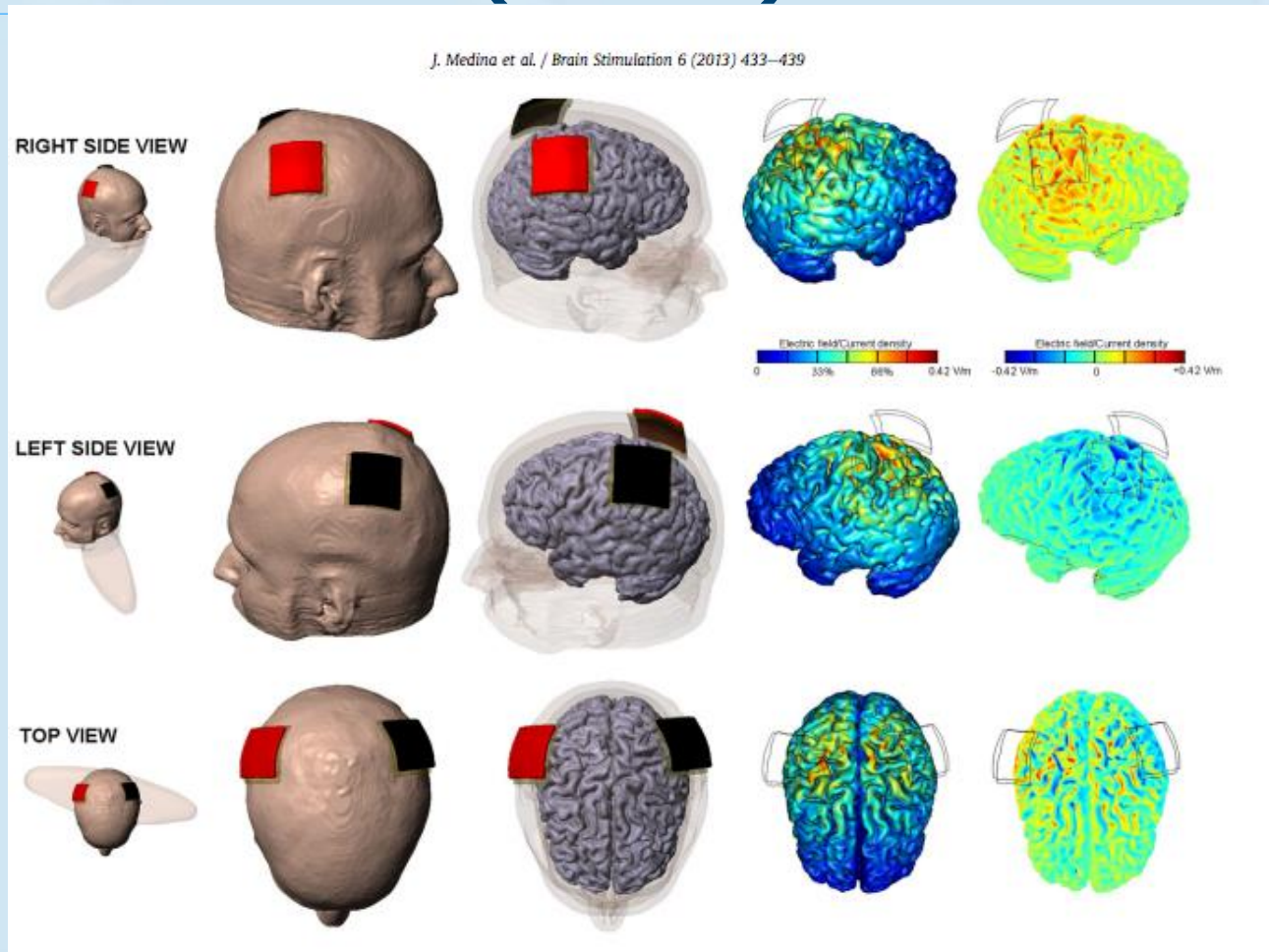
TENS should be considered for the treatment of painful diabetic neuropathy (**Level B**, two Class II studies).



# Brain stimulation has no proven efficacy (or safety) in RLS



# Transcranial direct current stimulation (tDCS)



# Transcranial direct current stimulation on primary sensorimotor area has no effect in patients with drug-naïve restless legs syndrome: a proof-of-concept clinical trial

Yong Seo Koo <sup>a</sup>, Sung Min Kim <sup>a</sup>, Chany Lee <sup>b</sup>, Byeong Uk Lee <sup>b</sup>, Ye Ji Moon <sup>b</sup>,  
Yong Won Cho <sup>c</sup>, Chang-Hwan Im <sup>d</sup>, Jeong Woo Choi <sup>e</sup>, Kyung Hwan Kim <sup>e</sup>,  
Ki-Young Jung <sup>b,\*</sup>

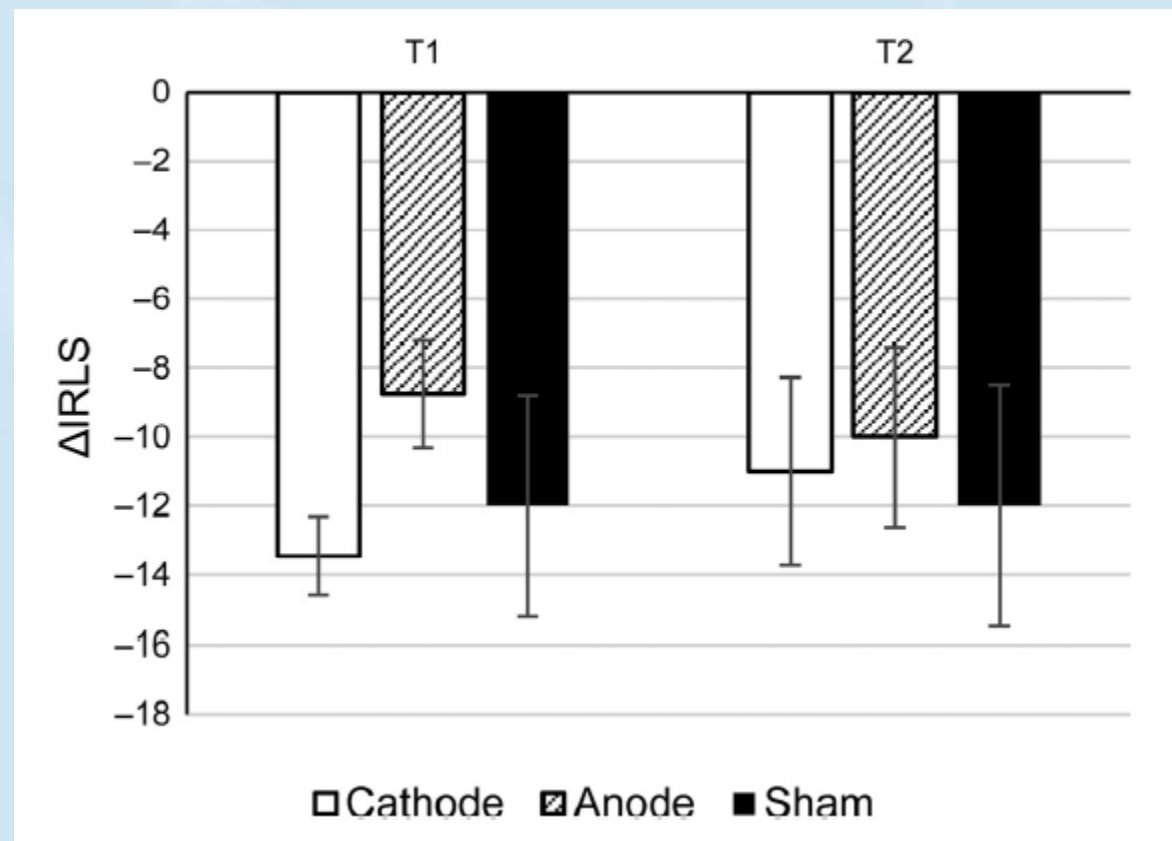
- Double-blind, sham-controlled, parallel group study in 33 subjects with severe RLS
- C<sub>z</sub> anodal (stimulating), cathodal (inhibiting) or sham stimulation of 2.5 mA for 20 minutes (sham=30 seconds only) at five time points over 2 weeks



# Transcranial direct current stimulation on primary sensorimotor area has no effect in patients with drug-naïve restless legs syndrome: a proof-of-concept clinical trial

Yong Seo Koo <sup>a</sup>, Sung Min Kim <sup>a</sup>, Chany Lee <sup>b</sup>, Byeong Uk Lee <sup>b</sup>, Ye Ji Moon <sup>b</sup>,  
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No significant efficacy for anodal or cathodal transcranial direct stimulation at C<sub>Z</sub>



# Effects of Transcutaneous Spinal Direct Current Stimulation in Idiopathic Restless Legs Patients

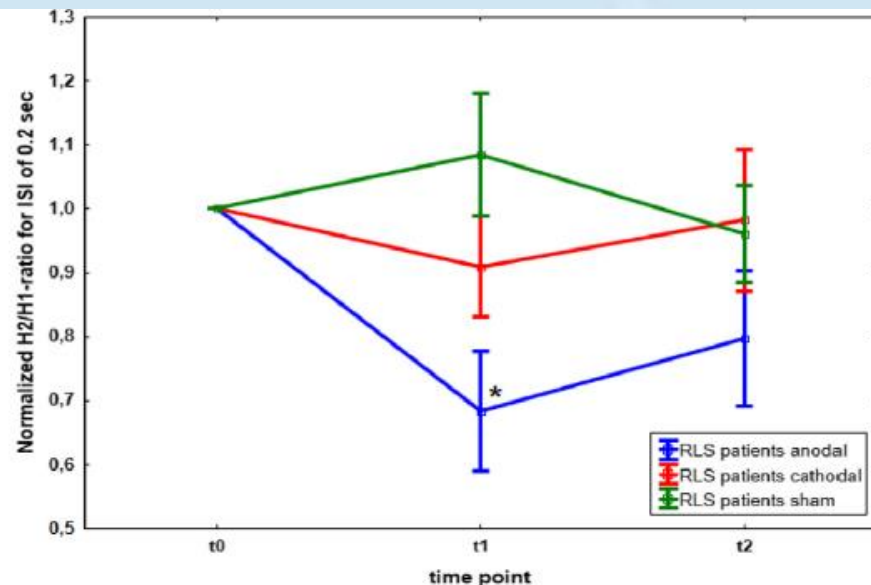
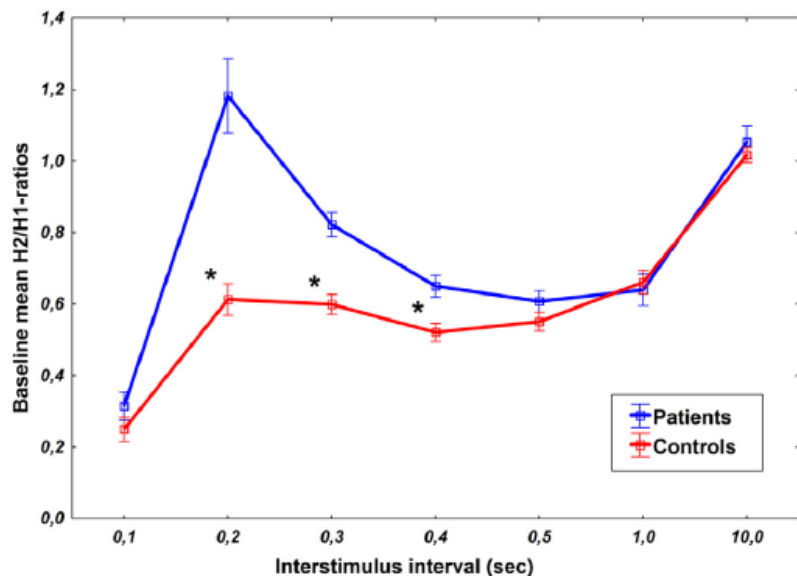
A.C. Heide<sup>a</sup>, T. Winkler<sup>d</sup>, H.J. Helms<sup>b</sup>, M.A. Nitsche<sup>a</sup>, C. Trenkwalder<sup>a,c</sup>, W. Paulus<sup>a</sup>, C.G. Bachmann<sup>a,e,\*</sup>

Brain Stimulation, 2014 7:636-642.

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- Double-blind, sham-controlled, crossover study in 20 subjects with severe RLS
- Paravertebral anodal (stimulating), cathodal (inhibiting) or sham stimulation of 2.5 mA for 30 minutes (sham=40 seconds only) at T11

# Anodal transcutaneous spinal stimulation reduces hyperexcitability in RLS



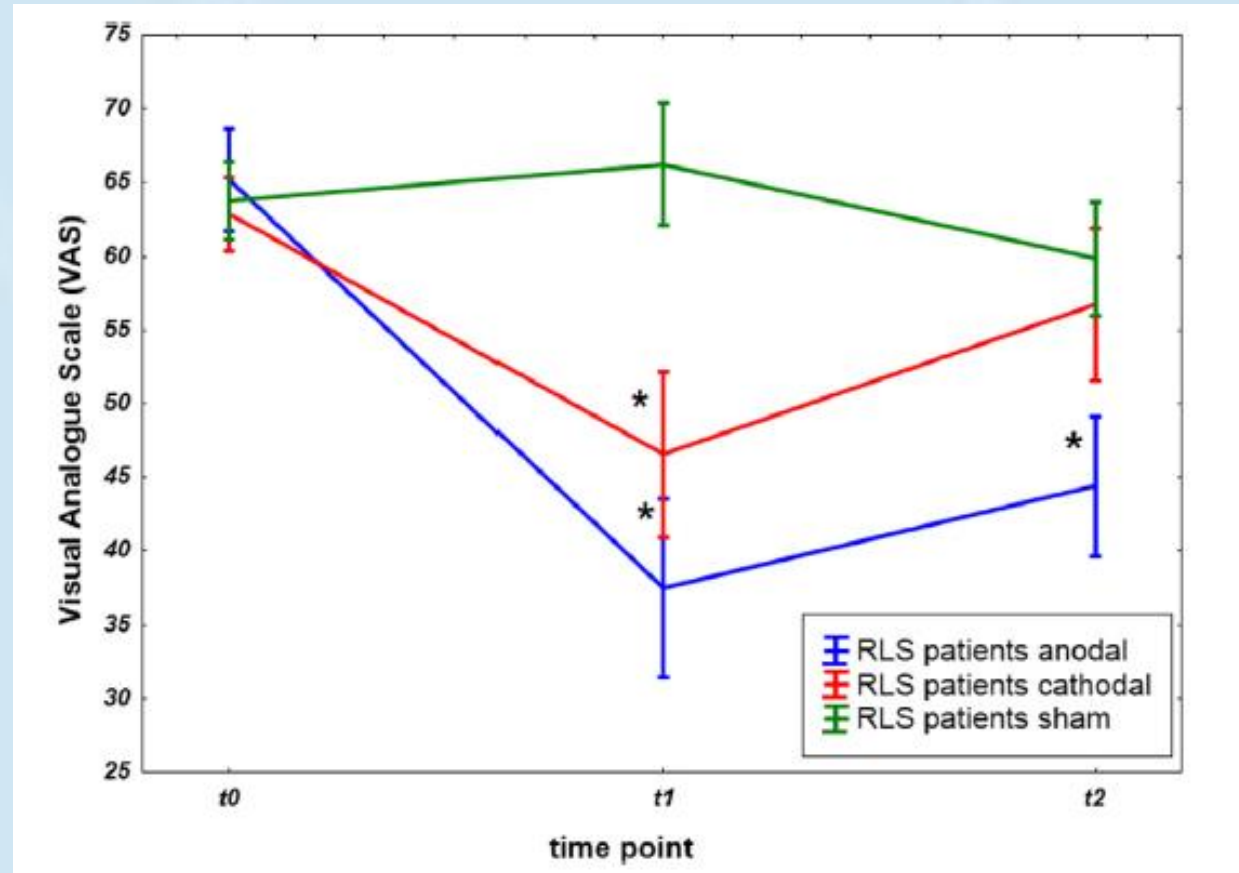
- H reflex is a monosynaptic reflex seen after stimulating the tibial nerve and recording from the calf
- H1 is the first activation; H2 is the activation after the second stimulation
- Elevated H2/H1 ratio seen in RLS is decreased by anodal transcutaneous spinal stimulation

# Effects of Transcutaneous Spinal Direct Current Stimulation in Idiopathic Restless Legs Patients

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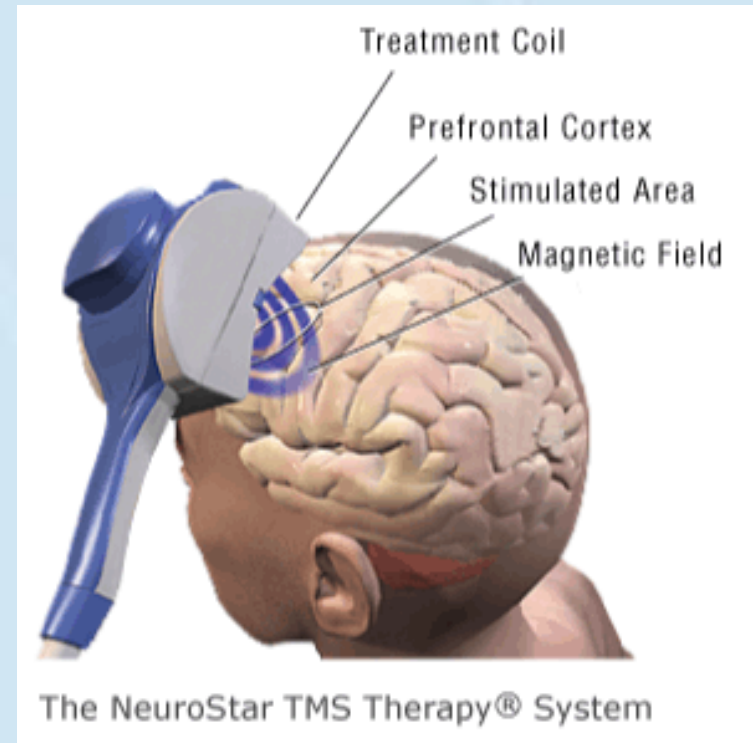
Benefit of anodal stimulation 30 minutes after stimulation





# Transcranial magnetic stimulation (TMS)

- Repetitive TMS is a non-invasive method to stimulate cortical tissues electrically by electromagnetic induction.
- Pulsatile electrical current is passed through a coil which generates a magnetic field oriented orthogonally to the plane of the coil.



# Repetitive transcranial magnetic stimulation in restless legs syndrome: preliminary results

Burcu Altunrende · Serpil Yildiz · Ayse Cevik ·  
Nebil Yildiz

Neurol Sci (2014) 35:1083–1088

- Single-blind, sham-controlled, parallel group study in 19 subjects with RLS
- Transcranial magnetic stimulation (TMS) at 5 Hz for 1000 stimuli at 110% of the resting motor threshold every 3 days for 1 month to the supplementary motor area



# Repetitive transcranial magnetic stimulation in restless legs syndrome: preliminary results

Burcu Altunrende · Serpil Yildiz · Ayse Cevik ·  
Nebil Yildiz

Neurol Sci (2014) 35:1083–1088

	Sham stimulation group (n:8)	Real stimulation group (n:11)
IRLS-RS scores baseline		
Mean ± SD	29.6 ± 3.3	31.7 ± 3.0
Median	30	33
Range	25–34	25–35
IRLS-RS scores after 5 session		
Mean ± SD	28.6 ± 3.3	19.1 ± 3.9
Median	29	19
Range	23–33	14–25
	<i>p</i> = 0.033 (between 0 and 5)	<i>p</i> = 0.003 (between 0 and 5)
IRLS-RS scores after 10 session		
Mean ± SD	28.6 ± 3.8	12.7 ± 5.1
Median	28.5	15
Range	24–35	3–19
	<i>p</i> = 0.086 (between 0 and 10) <i>p</i> = 0.931 (between 5 and 10)	<i>p</i> = 0.003 (between 0 and 10) <i>p</i> = 0.003 (between 5 and 10)



# Repetitive Transcranial Magnetic Stimulation for the Treatment of Restless Legs Syndrome

Yi-Cong Lin<sup>1,2</sup>, Yang Feng<sup>3</sup>, Shu-Qin Zhan<sup>1,2</sup>, Ning Li<sup>1,2</sup>, Yan Ding<sup>1,2</sup>, Yue Hou<sup>1,2</sup>, Li Wang<sup>1,2</sup>, Hua Lin<sup>1,2</sup>, Ying Sun<sup>1,2</sup>, Zhao-Yang Huang<sup>1,2</sup>, Qing Xue<sup>1,2</sup>, Yu-Ping Wang<sup>1,2,4</sup>

Chinese Medical Journal | July 5, 2015 | Volume 128 | Issue 13

- Open label study in 14 subjects with RLS
- TMS at 7.5 Hz for 600 stimuli at 100% of the resting motor threshold for 14 sessions over 3 weeks bihemispherically to the motor area

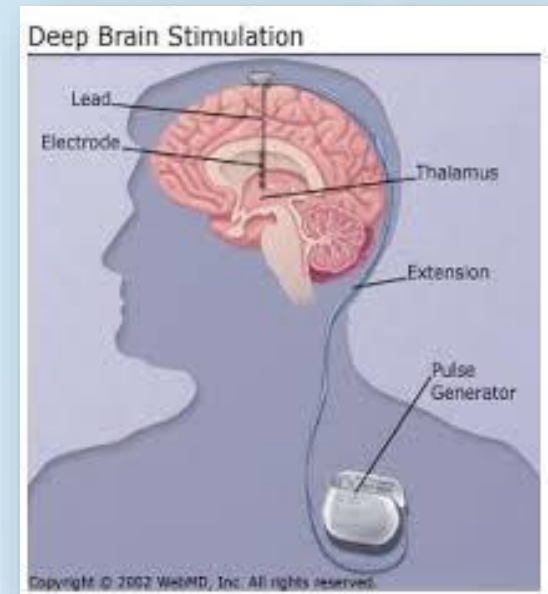
**Table 1: The IRLS-RS, PSQI, HAMA, and HAMD scores in the fourteen idiopathic RLS patients**

Time points	IRLS-RS		PSQI scores		HAMA scores		HAMD scores	
	Scores	<i>P</i> value	Scores	<i>P</i> value	Scores	<i>P</i> value	Scores	<i>P</i> value
Baseline	23.86 ± 5.88		15.00 ± 4.88		17.93 ± 7.11		15.43 ± 7.51	
End of 14 <sup>th</sup> session	11.21 ± 7.23*	0.000	9.29 ± 3.91*	0.000	10.36 ± 7.13*	0.024	8.14 ± 5.85	0.156
1 month post-treatment	11.57 ± 6.84*	0.000	9.07 ± 4.01*	0.003	8.36 ± 6.87*	0.003	7.93 ± 5.78	0.135
2 month post-treatment	14.36 ± 7.71*	0.003	9.64 ± 5.11*	0.009	9.79 ± 7.86*	0.012	7.57 ± 6.51	0.108



# Deep brain stimulation for RLS

- DBS of the globus pallidus internus (GPi) led to mixed improvement in RLS in 1 patient with refractory RLS (*Ondo et al, 2012, Sleep Med*)
- Case report of benefit of DBS of GPi for RLS (eg *Okun et al, 2005, Mov Disorders*) and mixed results of DBS of sub thalamic nucleus in Parkinson's Disease



# Transcutaneous electrical nerve stimulation (TENS) for RLS

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- Stimulate over tibial nerve
- Open label study in 9 subjects with RLS
- TENS for variable time per day (mean=3.6 hrs) at self-selected intensity above sensory threshold for 30 days at home to lateral lower leg
- 6/9 were CGI responders; IRLS (n=9): 19.6 → 13.3



*Winkelman et al, APSS, 2016*

# Vibratory stimulation in RLS

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Mode of action may be either:

neural (counter stimulation) or

vascular (dilate blood vessels and increased oxygen supply)



Pneumatic compression



Vibration

# Pneumatic Compression Devices Are an Effective Therapy for Restless Legs Syndrome\*

**A Prospective, Randomized, Double-Blinded, Sham-Controlled Trial**

*Christopher J. Lettieri, MD, FCCP; and Arn H. Eliasson, MD, FCCP*

**(CHEST 2009; 135:74–80)**



AAN Guidelines (Winkelman et al, 2016): “Pneumatic compression is likely effective in the treatment of patients with primary moderate to severe RLS”

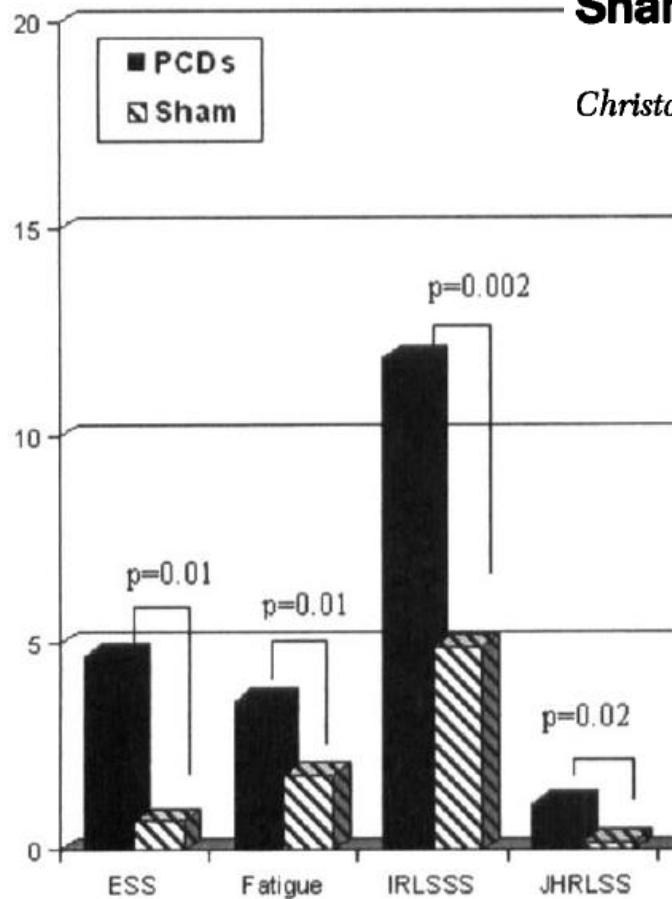


# Pneumatic Compression Devices Are an Effective Therapy for Restless Legs Syndrome\*

## A Prospective, Randomized, Double-Blinded, Sham-Controlled Trial

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(*CHEST* 2009; 135:74–80)



# Sleep improvement for restless legs syndrome patients. Part I: pooled analysis of two prospective, double-blind, sham-controlled, multi-center, randomized clinical studies of the effects of vibrating pads on RLS symptoms

Journal of Parkinsonism and Restless Legs Syndrome

- Two double-blind, sham-controlled, parallel studies in 168 subjects with moderate-severe RLS
- Vibrating pad or sham (light or sound) stimulation for 35 minutes under the leg(s) at home



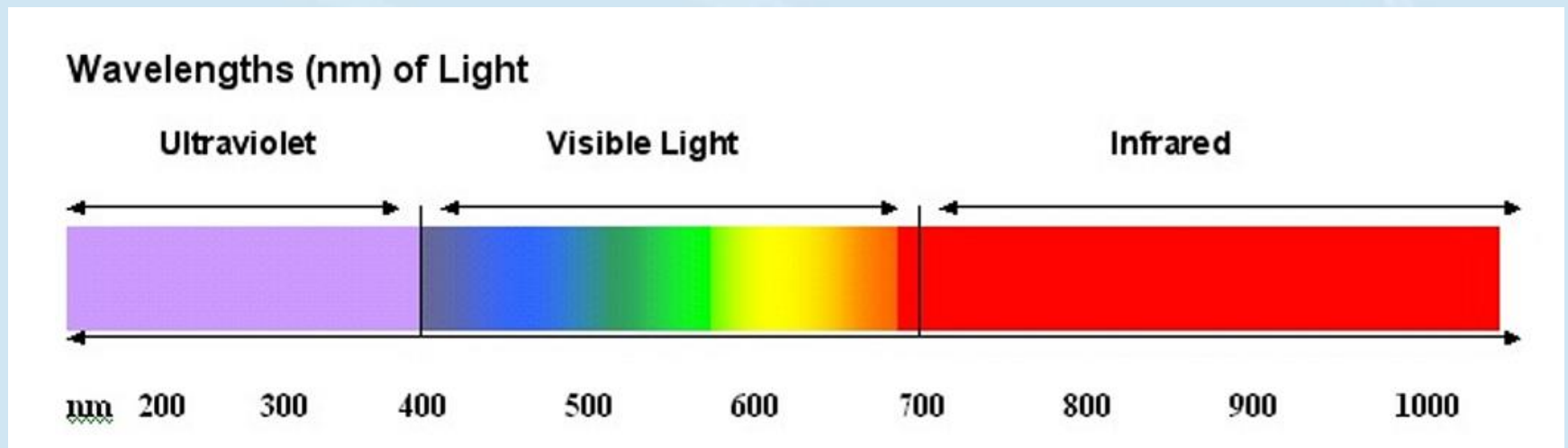
# Sleep improvement for restless legs syndrome patients. Part I: pooled analysis of two prospective, double-blind, sham-controlled, multi-center, randomized clinical studies of the effects of vibrating pads on RLS symptoms

	<b>IRLS scores</b>	<b>RLS-QoL scores</b>	<b>MOS-II scores</b>
Vibrating pad patients (SD)	-6.68 (7.28)	11.14 (17.98)	-13.29 (19.67)
Sham pad patients (SD)	-6.39 (7.50)	7.01 (15.52)	-6.20 (15.69)
(Vibration – sham) differences (95% CI)	-0.29 (-2.66 to 2.08)	4.13 (-1.33 to 9.59)	-7.09 (-12.92 to -0.27)
% superiority vibration over sham	4.5%	58.9%	114.4%
P-values	0.81	0.14	0.02

**No efficacy of vibrating pads for RLS, though sleep did improve**

# Near-infrared stimulation

*Physiother Theory Pract. 2010;27(5):352–359.*



Proposed mechanism of action is increased blood flow in the stimulated area

# Near-infrared stimulation

*Physiother Theory Pract. 2010;27(5):352–359.*

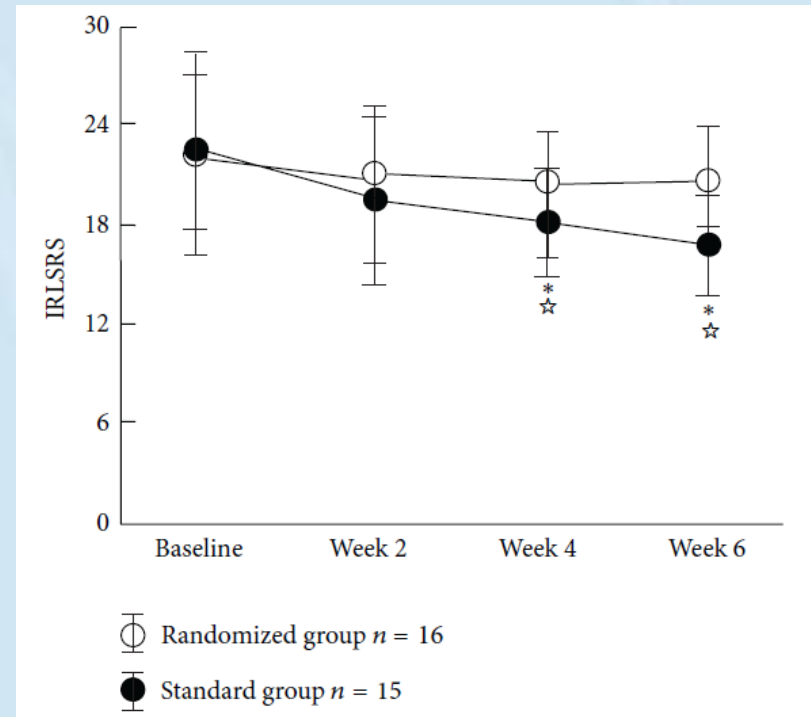
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- Double-blind, sham-controlled, parallel group study in 34 subjects with mild RLS
- Twelve 30-minute treatments to lower legs for 4 weeks
- There was a greater reduction in the IRLS score at 4 weeks with NIRS (mean difference between groups -8.3, 95% CI -12.3 to -4.3)



# Actigraph Evaluation of Acupuncture for Treating Restless Legs Syndrome

- Single-blind, sham-controlled, parallel group study in 38 subjects with moderate-severe RLS
- 30-minute treatments 3x/wk to localized or random (sham) sites for 6 weeks



Evidence-Based Complementary and Alternative Medicine  
Volume 2015, Article ID 343201, 7 pages



# Summary

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RLS is a neurological disorder with underlying hyper excitability at multiple levels of the nervous system

Electrical or other forms of non-pharmacological stimulation may be able to diminish hyperexcitability in some RLS patients by the same mechanism that movement does or by an alternative pathway



# Question & Answer

*For more information about upcoming webinars & events visit:  
[www.rls.org/get-involved/education-events](http://www.rls.org/get-involved/education-events)*

