Neuromodulation Devices for Migraine Treatment

Natalia Murinova, MD
Clinical Professor Neurology
Director of the Headache Clinic UW
Director of the Headache Fellowship UW
ACP Washington Conference 2024

Incorporating Neuromodulation Devices for Headache Management

- Natalia Murinova, MD
- UW Headache Clinic

Overview

Multimodal Treatment Approach

Focus on Neuro-Modulation Devices: Focus on CEFALY and Nerivio

- Mechanisms
- Considerations / contraindications
- How to prescribe

Case throughout

Patient Jane

Jane

- **Headache Profile**: 45-year-old female with ~6 monthly attacks, lasting 6 hours if untreated; moderate-severe, right-sided pain worsened by movement, with photophobia and nausea.
- **Treatment History**: Over-the-counter medications (ibuprofen, naproxen, Excedrin) provide ~75% symptom relief but do not fully resolve headaches.
- **Impact on Function**: Headaches result in ~2 missed workdays per month

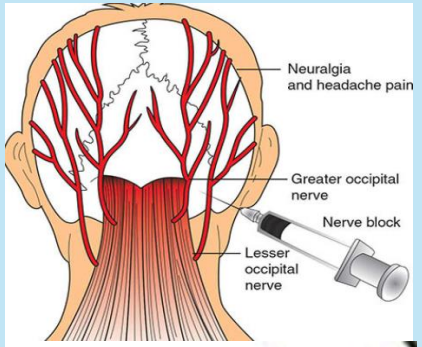
Jane

- You ask Jane what kinds of treatments she is interested in pursuing.

- She prefers “no medications”

Non-Medication Multimodal Treatment Approach

- **Both medication and non-medication approaches have evidence for treatment of migraine.**
  - Support Sleep
  - Manage Stress
  - Exercise
  - Supplements
  - Procedures
  - Nutrition
  - Neuromodulation



Non-Medication Multimodal Treatment Approach

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  - Support Sleep
  - Manage Stress
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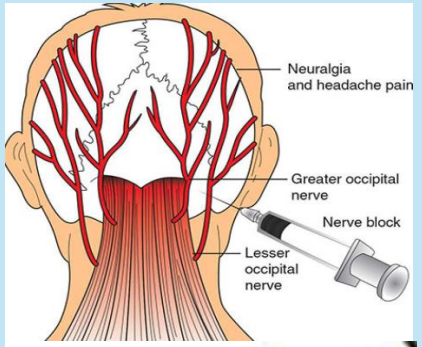
  - Procedures
  - Nutrition
  - **Neuromodulation**



Neuromodulation Devices

- **What is Neuromodulation?**
  - Umbrella term
  - Technique used to **alter the activity of the nervous system**
  - Background:
    - Brain function is **electrical activity**
    - Many disorders result from the brain functioning out of “normal range”
  - Goal of neuromodulation = **normalize the brain function**

Relivion

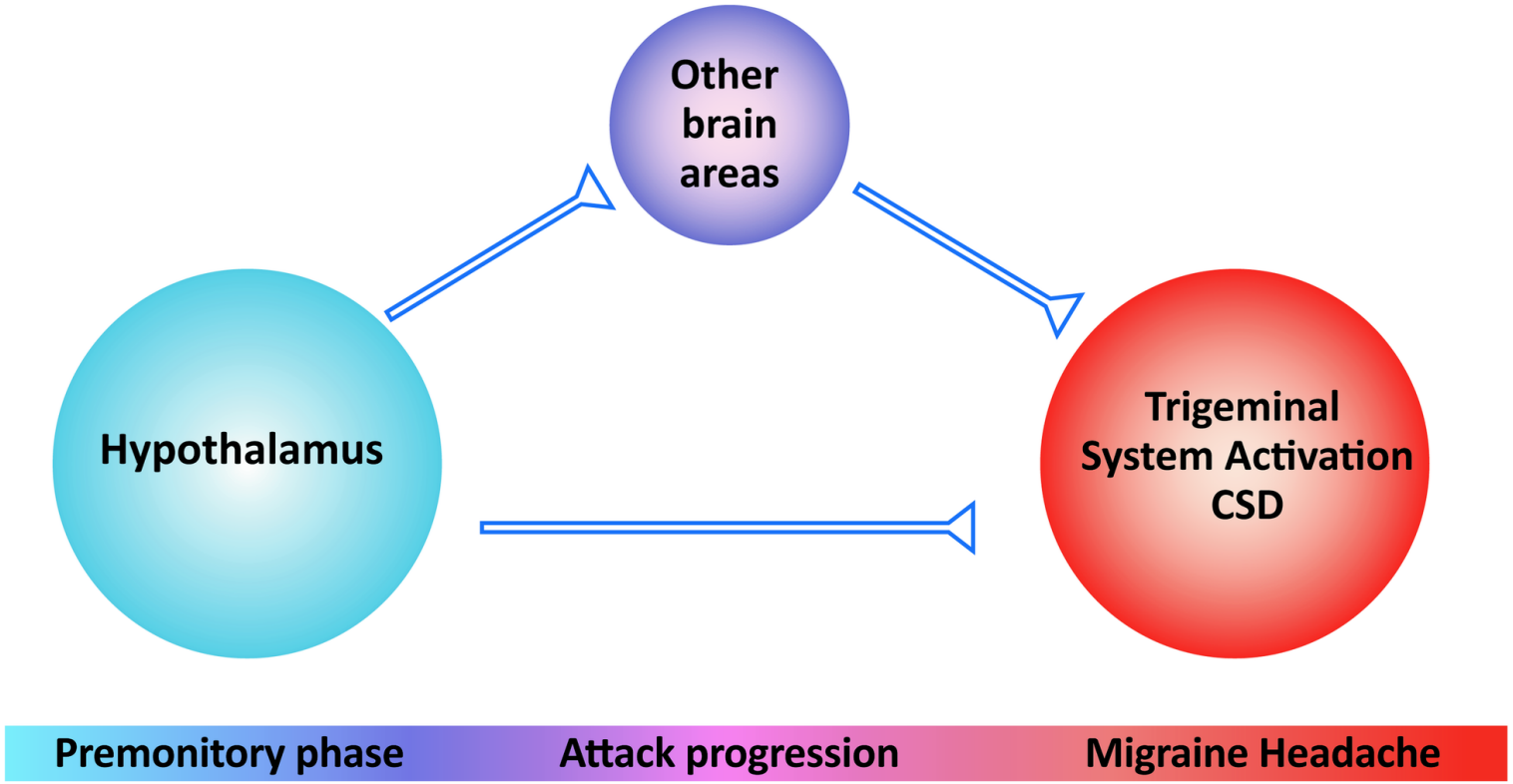
gammaCore

CEFALY

Nerivio

Neuromodulation Devices: How They Work

- Recall that migraine pathophysiology involves changes in electrochemical activation in the brain



Neuromodulation Devices

- Neuromodulation for headache management is a **therapeutic approach that involves altering nerve activity within the brain and nervous system to reduce headache pain and frequency**

Neuromodulation Devices

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- Mechanism:
  - Delivery of **electrical or magnetic stimulation** to specific areas of the brain or peripheral nerves → modulation of pain pathways involved in headaches → changing the way the brain perceives and responds to headache pain

Neuromodulation Devices

- Neuromodulation for headache management is a **therapeutic approach that involves altering nerve activity within the brain and nervous system to reduce headache pain and frequency**
- Mechanism:
  - Delivery of **electrical or magnetic stimulation** to specific areas of the brain or peripheral nerves → modulation of pain pathways involved in headaches → changing the way the brain perceives and responds to headache pain
- Techniques: Variable! May include:
  - External trigeminal nerve stimulation
  - Occipital nerve stimulation
  - Vagal nerve stimulation
  - Remote electrical neuromodulation.

Case: Jane

- Jane is interested in neuromodulation devices.
- She wonders if she would a candidate for one of them.

Neuromodulation Devices

Is Jane a candidate?
Which patients can neuromodulation help?

Neuromodulation Devices

- **Almost everyone!**
- Patients who are looking to **bolster their acute and preventive approaches** for treatment of migraine
- Patients **at risk for medication overuse** headache (due to headache or other body pain)
- Patients who **prefer not to use medications**/injections
- Patients with **medical conditions** preventing them from taking traditional medications for headache
- Patients who have **limited access/interest in acute care services** for severe headache
- ≥ 18 years old

Case: Jane

- Jane wants to try to the device that was established first and has the most evidence.

Neuromodulation Devices

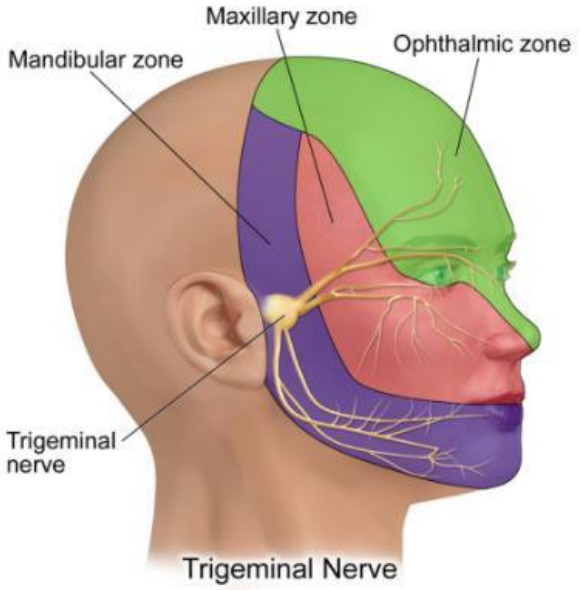
Which was the first neuromodulation device developed for migraine?

Neuromodulation Devices: CEFALY

- **CEFALY**
  - First device to use transcutaneous stimulation for targeted treatment of migraine.
  - FDA-cleared for treatment of migraine in 2014
  - Mechanism: External trigeminal neurostimulation (eTNS) device

Neuromodulation Devices: CEFALY

- **How does CEFALY work?**
  - The device consists of an **electrode with skin adhesive** placed on the forehead covering the sites of the supraorbital and supratrochlear nerves, both of which are branches of the ophthalmic nerve (or the first branch of the trigeminal nerve).



Neuromodulation Devices: CEFALY

- **How strong is the CEFALY impulse?**
  - CEFALY generates biphasic rectangular impulses with **high frequency of 60Hz** and **low intensity of 16 mA.** This is aimed to **avoid crossing the pain threshold while still being able to activate Aβ afferents and leading to paresthesia in the distribution of the nerve and preventing the activation of Aδ and C fibers important in nociception and reducing hyperalgesia.**

- CEFALY is a **constant current generator** that delivers pulses (100 Hz)
- The intensity increases linearly to reach a maximum of 16 mA after 14 min → constant 46 min

Neuromodulation Devices: CEFALY

- **How strong is the CEFALY impulse?**

- Magnetic field produced: < 0.2µT is **negligible** compared to the field generated by:
  - An electric shaver (typically 15-1500µT)
  - A hair dryer (typically 6-2000µT)

Case: Jane

- Jane is open to trying Cefaly, however she wonders if this is an acute or preventive treatment for migraine?

Neuromodulation Devices: CEFALY

Is CEFALY an acute or preventive treatment?

Neuromodulation Devices: CEFALY

- **Both!**
- Acute: 1 hour session
- Preventive: 20 minutes daily
  - Can be worn at any time of day, but evening may be preferred
  - Turns off automatically after the session

Case: Jane

- Jane wonders what it will feel like to have a Cefaly on her head.

Neuromodulation Devices: CEFALY

What does a person feel when wearing CEFALY?

Neuromodulation Devices: CEFALY

- Patient may feel **nothing** or a **slight tingling sensation**
- The sensation **increases gradually and spreads through the forehead and the front part of the head**
- **After 14 minutes, the intensity stabilizes and remains constant until the treatment session is over**

Case: Jane

- Jane asks, “Is CEFALY safe? Will the CEFALY fry my brain cells?”

Neuromodulation Devices: CEFALY

Is CEFALY safe?

Neuromodulation Devices: CEFALY

RESEARCH ARTICLE Open Access

Safety and patients' satisfaction of transcutaneous Supraorbital NeuroStimulation (tSNS) with the Cefaly® device in headache treatment: a survey of 2,313 headache sufferers in the general population

Delphine Magis*, Simona Sava, Tullia Sasso d'Elia, Roberta Baschi and Jean Schoenen

Neuromodulation Devices: CEFALY

- **Survey:**
  - n= 2,313 headache sufferers in the general population

- **Results:**
  - Only 4.3% of subjects reported AEs (**all minor and fully reversible)**

- **The most frequent AEs were local pain/intolerance to**
  - **paresthesia** (2.03%)
  - **arousal changes** (mostly sleepiness/fatigue, sometimes insomnia ; 0.82%)
  - **headache after the stimulation** (0.52%)
  - **a transient local skin allergy** (0.09%)

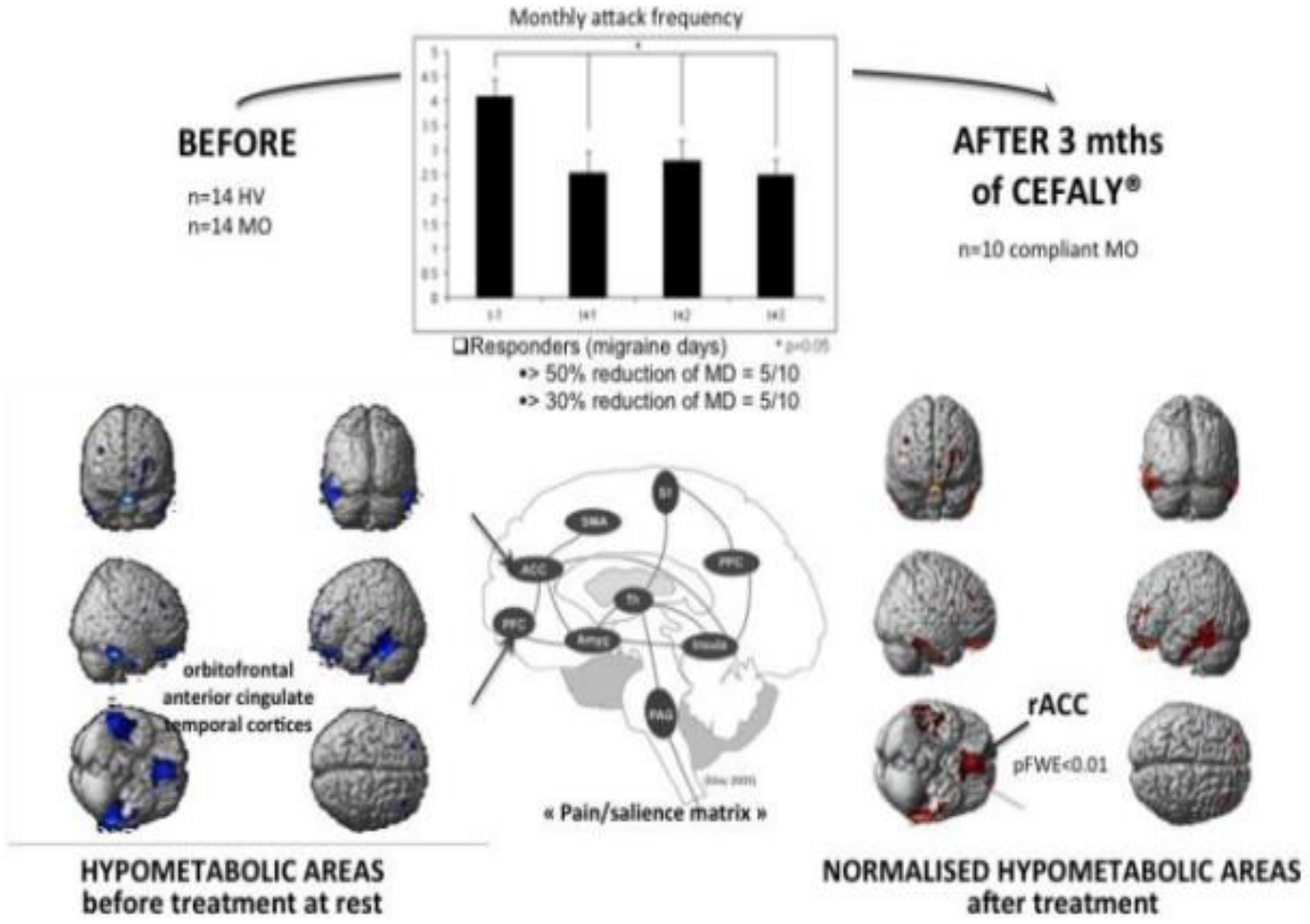
- **Conclusion:**
  - tSNS with is a **safe and well-tolerated treatment for migraine headaches** that provides satisfaction to a majority of patients who tested it for 40 days.

Neuromodulation Devices: CEFALY

What is the additional supporting data?

Neuromodulation Devices: CEFALY

- **Function:** CEFALY normalizes activity in cortical areas controlling pain and brain function

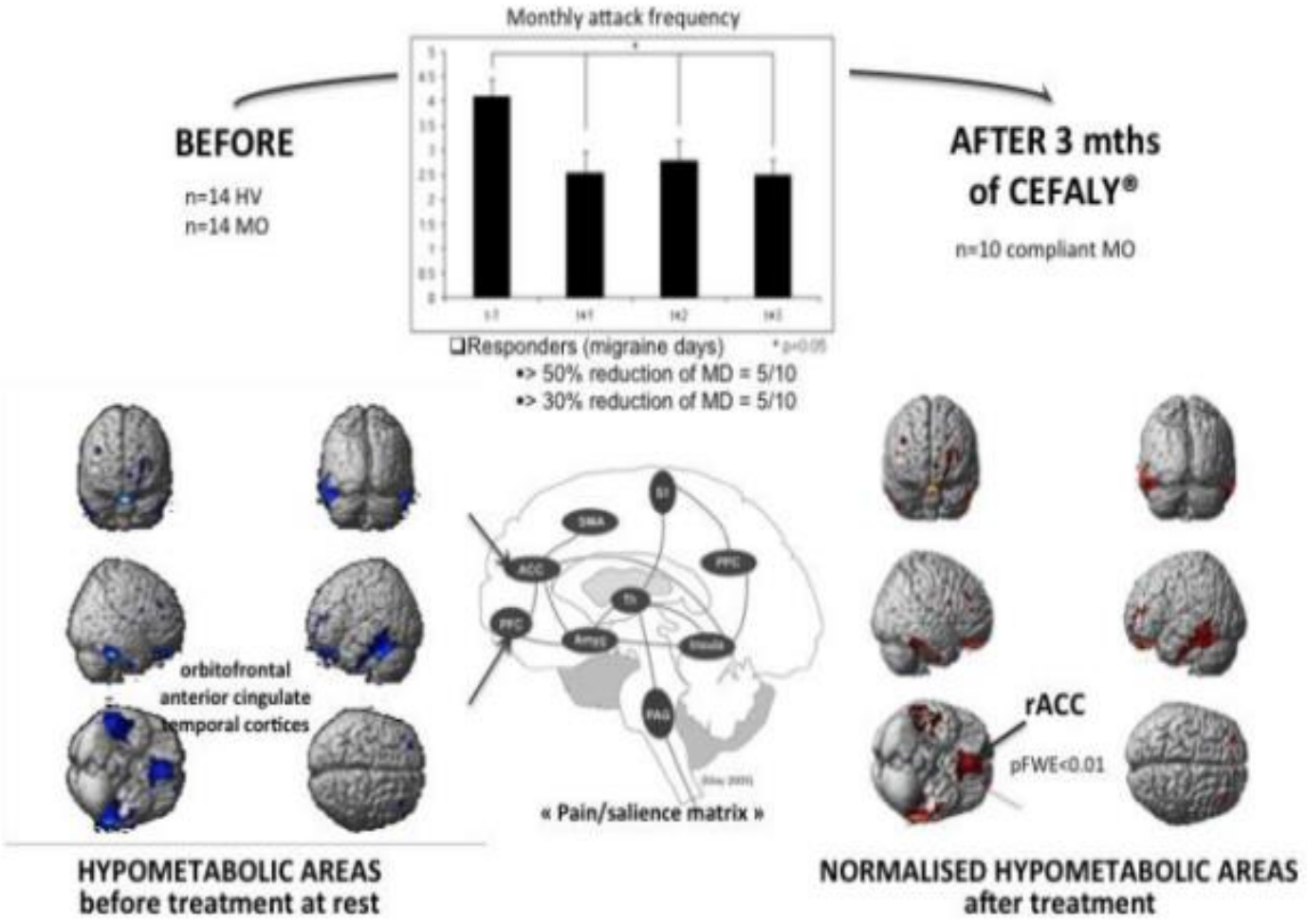


Ref: Schoenen J. Migraine treatment with external trigeminal nerve stimulation: current knowledge on mechanisms. Internal Medicine Reviews. 2017.

Neuromodulation Devices: CEFALY

- **Function:** CEFALY normalizes activity in cortical areas controlling pain and brain function

- <u>Single session during migraine attack:</u>
  Relieves pain transiently, but **no effect on cerebral metabolism**



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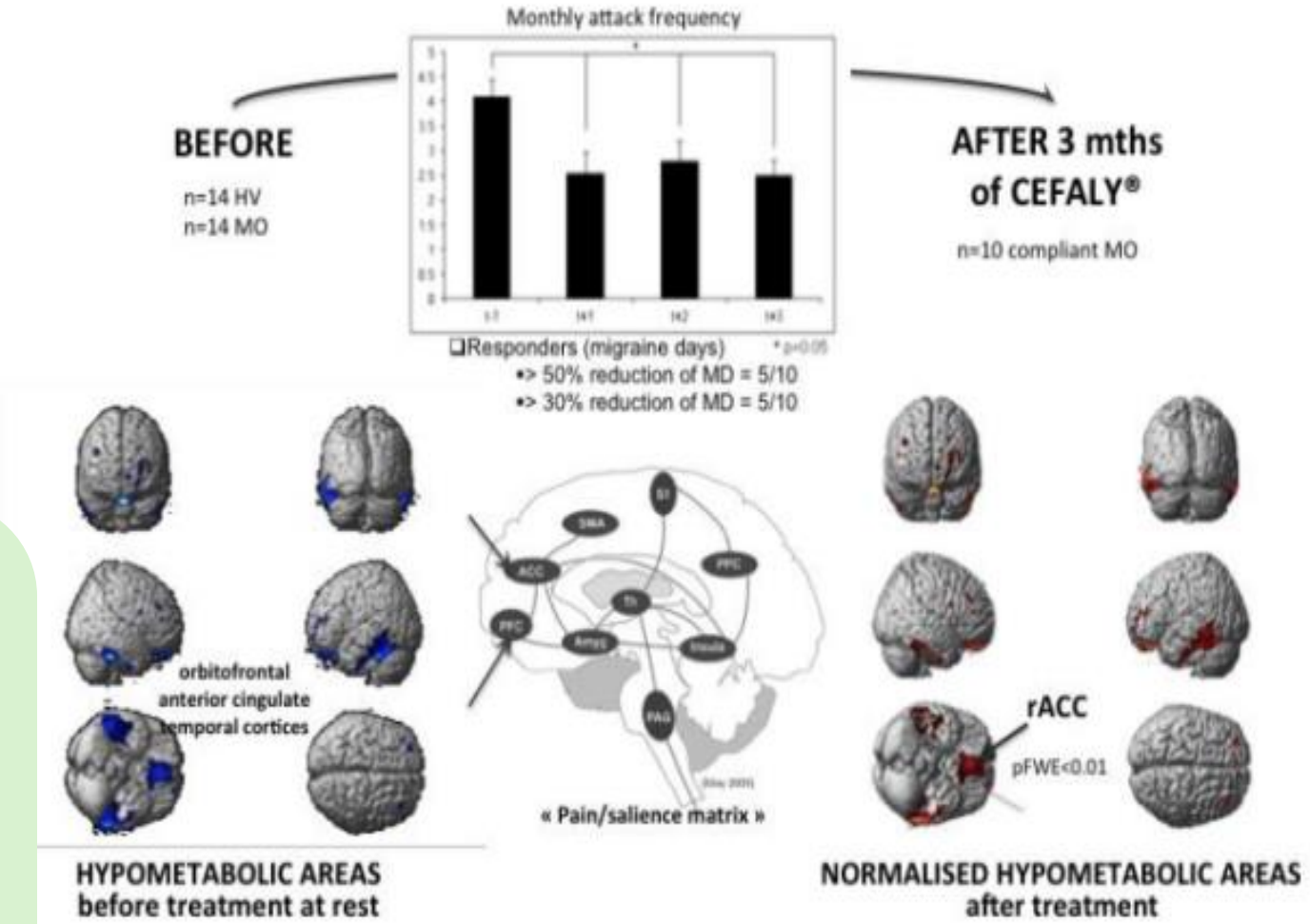
Neuromodulation Devices: CEFALY

- **Function:** CEFALY normalizes activity in cortical areas controlling pain and brain function

- Single session during migraine attack: **Relieves pain transiently**, but **no effect on cerebral metabolism**

- After several months: **Increased metabolism** assessed with FDP-PET in pre-treatment hypo-metabolic medial prefrontal cortical areas, including anterior cingulate cortex, while trigeminal noxious heat-induced fMRI BOLD hyper-activation normalizes
- **These metabolic changes are accompanied by a significant decrease in monthly attack frequency in compliant patients**



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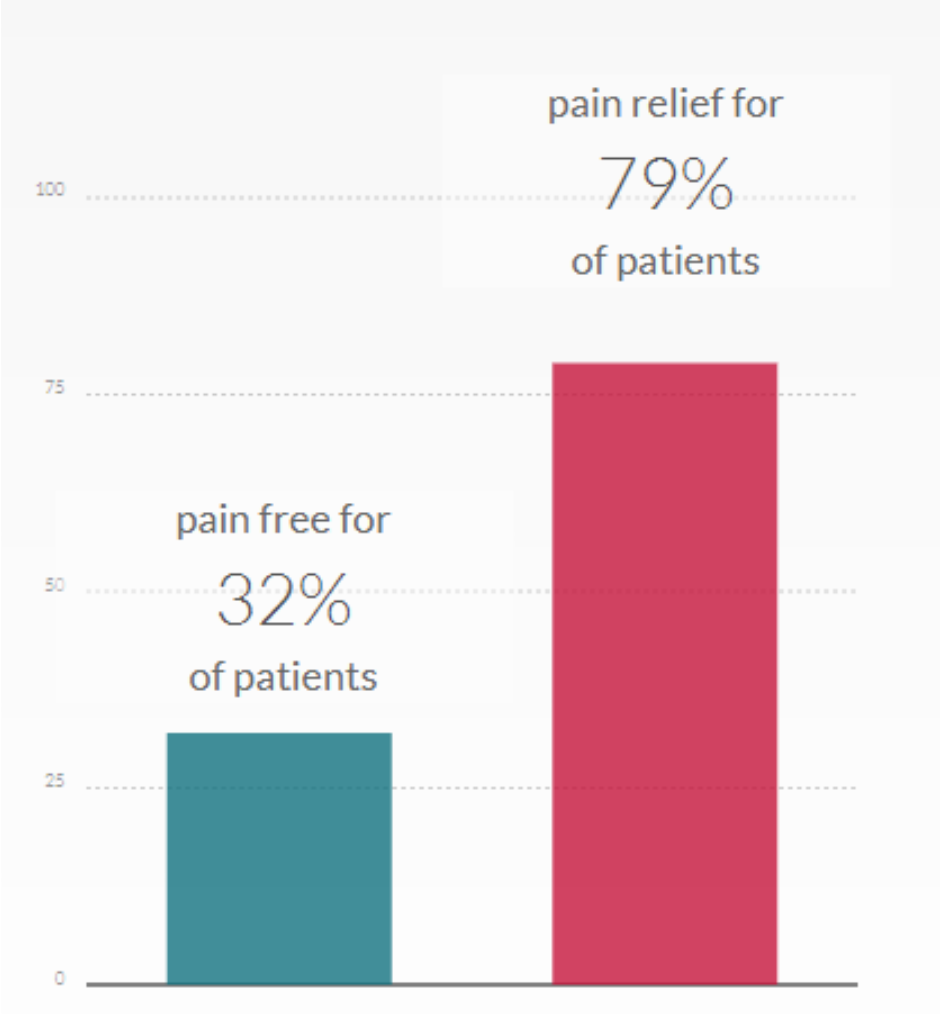
Case: Jane

- Jane asks, “What results can I expect if I start this device? How will CEFALY impact my headache frequency and severity?”

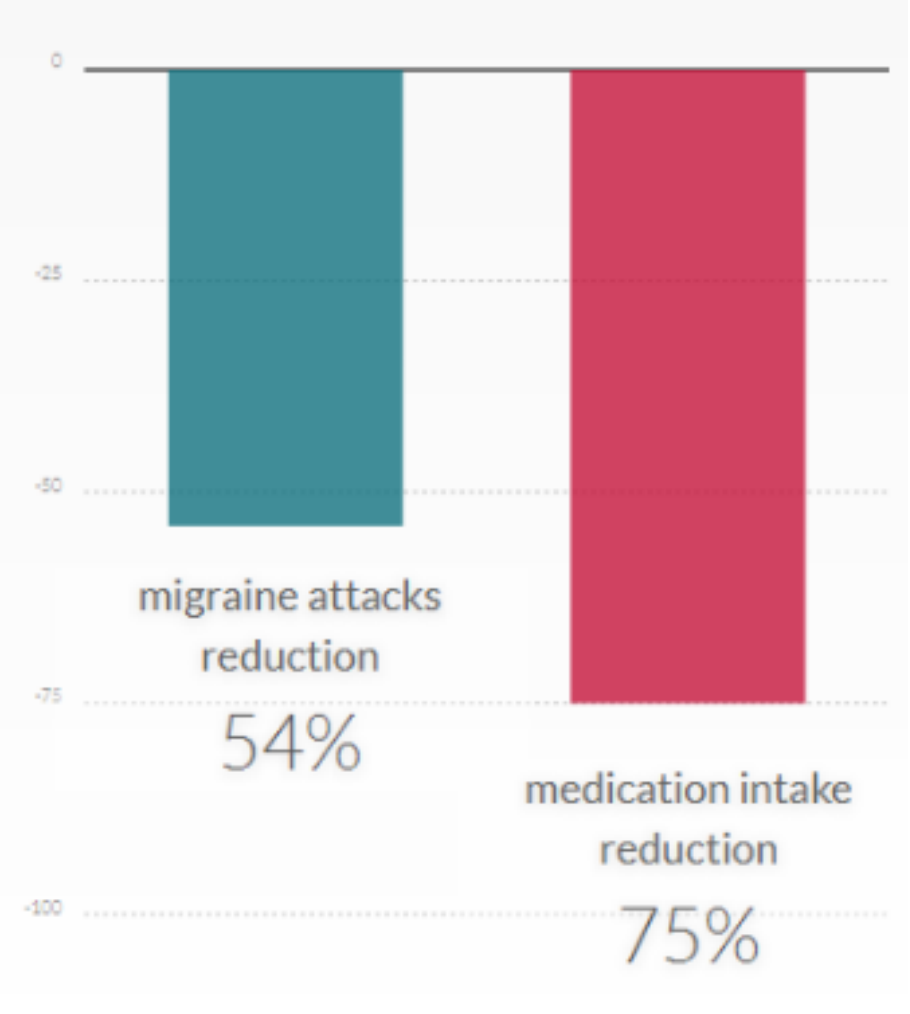
Neuromodulation Devices: CEFALY

What do the clinical trials show?

Neuromodulation Devices: CEFALY



Acute Management



Preventive Management

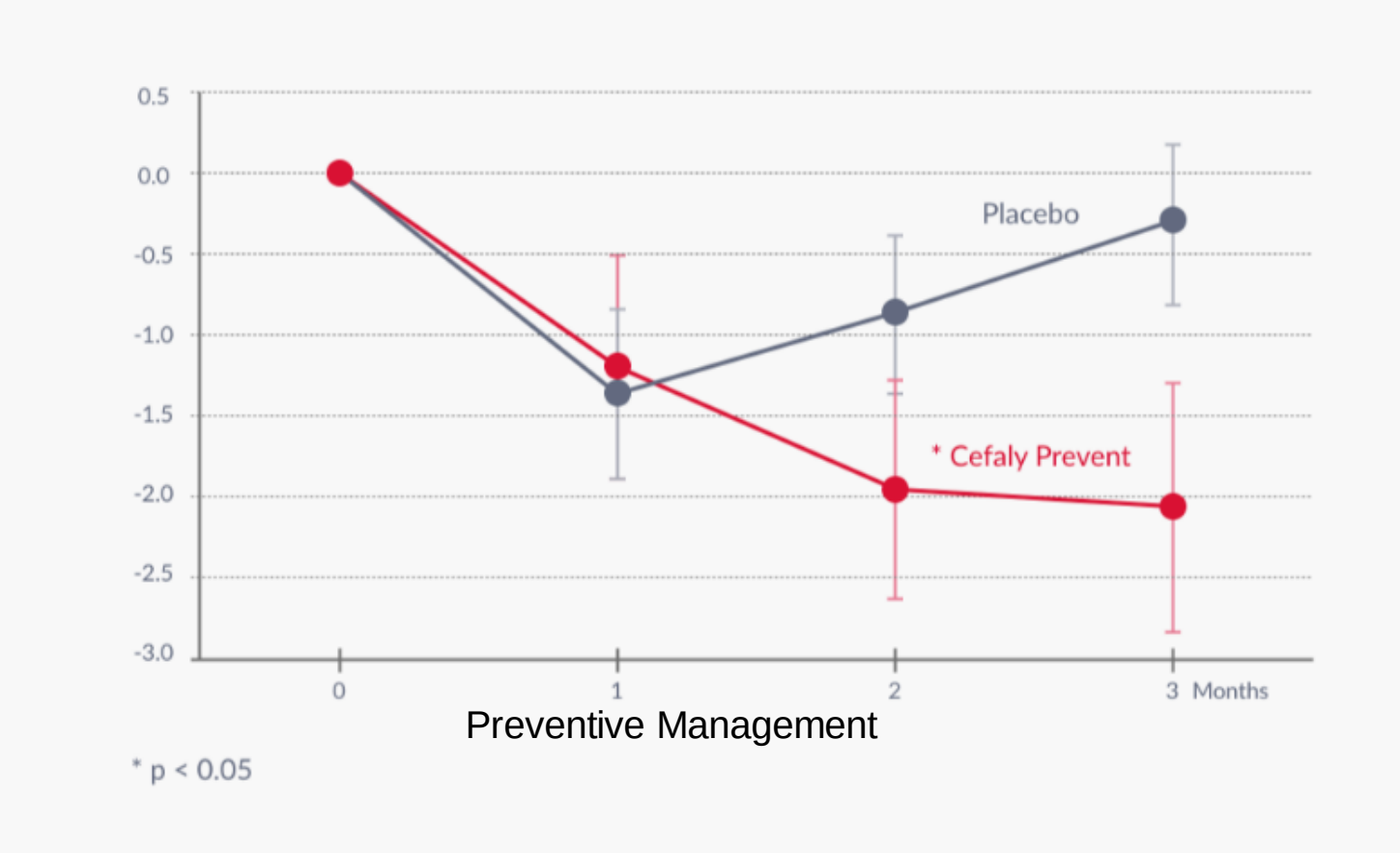
Reference: Chou D.E. et al. Acute migraine therapy with external trigeminal neurostimulation (ACME): A randomized controlled trial. Cephalalgia. 2018

Neuromodulation Devices: CEFALY

How do we know this is not just placebo effect?

Neuromodulation Devices: CEFALY

- **CEFALY vs placebo**



Reference: Jean Schoenen, Bart Vandersmissen, Sandrine Jeangette, Luc Herroelen, Michel Vandenheede, Pascale Gerard, Delphine Magis. Neurology Feb 2013, 80 (8) 697-704; DOI: 10.1212/WNL.0b013e3182825055

Neuromodulation Devices: CEFALY

- **Additional supporting data**
  - Several clinical trials since 2008
  - Available of CEFALY website

Acute treatment of migraine

Type of clinical study	Conclusion	Scientific publication
Double-blind versus placebo	Sedative effect	BMC Neurology 2011
Pilot open trial	Effective for acute treatment of migraine attacks	Neuromodulation 2017
Survey	Effective for users in "real world"	Acta Neurol Belg. 2017
Pivotal Randomized Double-blind versus placebo	Effective and safe for acute treatment of migraine attacks	Cephalalgia 2018
Pilot open trial	Effective for migraine abortion	Cephalalgia Reports 2019

Migraine Prevention

Type of clinical study	Conclusion	Scientific publication
Pivotal Randomized Double-blind versus placebo	Effective at preventing migraine	Neurology 2013
Cohort of 2300 patients	Best safety for migraine treatment	Journal of Headache and Pain 2013
Responders rate	First line treatment	Journal of Headache and Pain 2015
Prospective study on chronic migraine	Effective on chronic migraine	Neurological Sciences 2017
Prospective exploratory on refractory migraine	Effective on refractory migraine	BMC Neurology 2017
Open trial on chronic migraine	Effective on chronic migraine	Cephalalgia Reports 2019

Neurophysiology and Mechanism of action

Type of clinical study	Conclusion	Scientific publication
PET Scan	Central action of Cefaly	Cephalalgia 2016
Action mechanism	Current knowledge on mechanisms on trigeminal nerve	Internal Medicine Review 2017
fMRI	Central action of Cefaly	Frontiers in Neurology2017
Review	Previous data confirmation	Pain and Therapy journal 2015
Evoked Cortical Potential	Central action of Cefaly	Cephalalgia 2018
Review	Rationale for electrical parameters	Cephalalgia 2018

Case: Jane

- Jane asks, “Are there any long-term risks?”

Neuromodulation Devices: CEFALY

What are the longer-term data?

Neuromodulation Devices: CEFALY

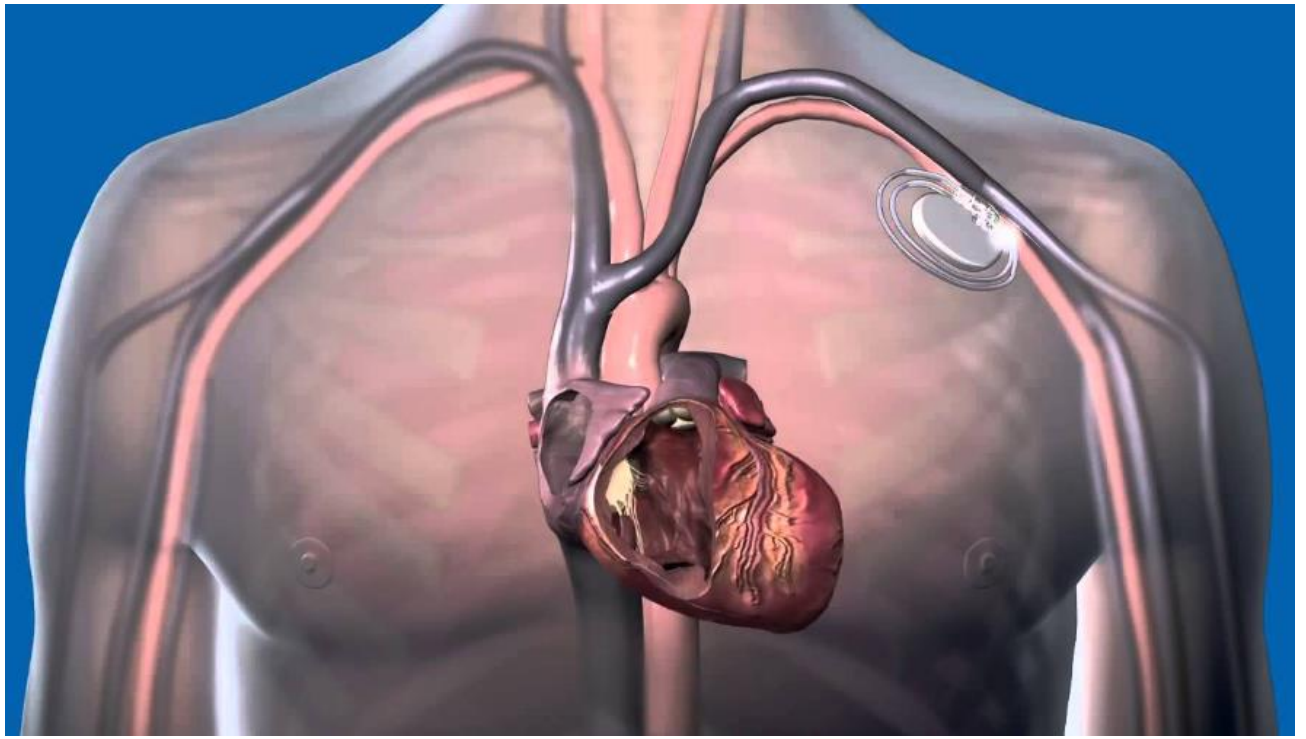
- Neurostimulation has been **used for > 20 years** (implanted devices that work constantly for years)
- The only problems with implantable neurostimulators relates to the surgical procedure to implant them, never to the neurostimulation technique itself
- Therefore, the technique is regarded as **exceptionally safe**

Case: Jane

- Jane states she would like to try CEFALY.
- What contraindications should you be aware of prior to starting this treatment for Jane?

Neuromodulation Devices: CEFALY

- **Contraindications:**
  - Implanted metallic or electronic device in the head
  - A cardiac pacemaker or implanted or wearable defibrillator (may cause interference with pacing, electric shock, or death.

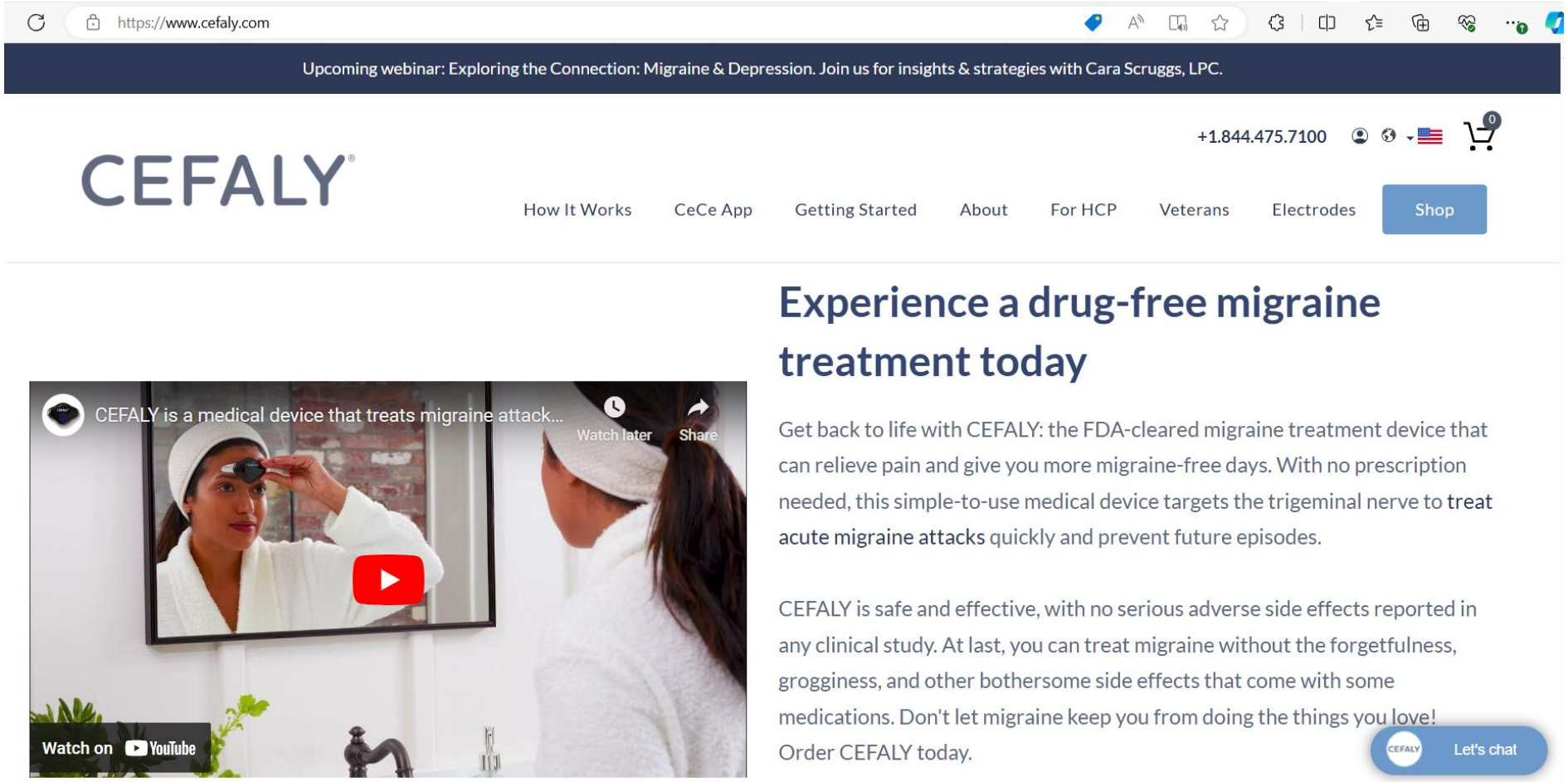


Case: Jane

- She does not have any contraindications.
- You order the device.

Neuromodulation Devices: CEFALY

- **How to order:**
  - Cefaly.com
  - 90 day return policy



Case: Jane

- Jane buys the CEFALY device and starts to use it. She finds the device is bothersome at full intensity and maybe even worsens her headaches.

- She asks you for tips for improving how it feels.

Case: Jane

- You explain the following tips:
  - After putting on the device, its intensity level can be stopped at a lower level by pressing the button.
  - She can use the device at a lower intensity for a period of time, and then gradually increase as tolerated to the full intensity.

Case: Jane

- Jane tries this approach and have benefit.
- Her headaches decrease in frequency by 50% after 3 months.

Case: Jane

- One year later, Jane re-presents to your clinic. She notes the gap in her care occurred because she had an insurance change (now on Blue Cross/Blue Shield).
- Her headaches have increased in frequency in the last few months.
- After a full evaluation including imaging, you are not concerned about a secondary etiology of headache and you discuss additional non-medication treatment options (still her preference).

Neuromodulation Devices: Nerivio

What other neuromodulation device should you consider?

Neuromodulation Devices: Nerivio

- **This one!**

Neuromodulation Devices: Nerivio

- **What is Nerivio?**
  - Remote electrical neuromodulation
  - Device worn on the arm
  - Controlled via smartphone app
    - App also contains migraine calendar

Case: Jane

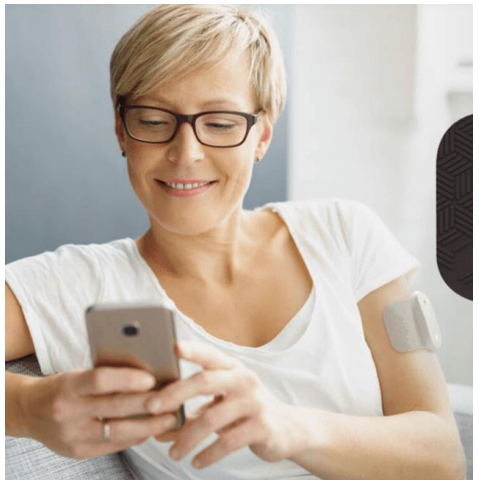
- Jane’s interest is piqued. She asks, “How does Nerivio work?

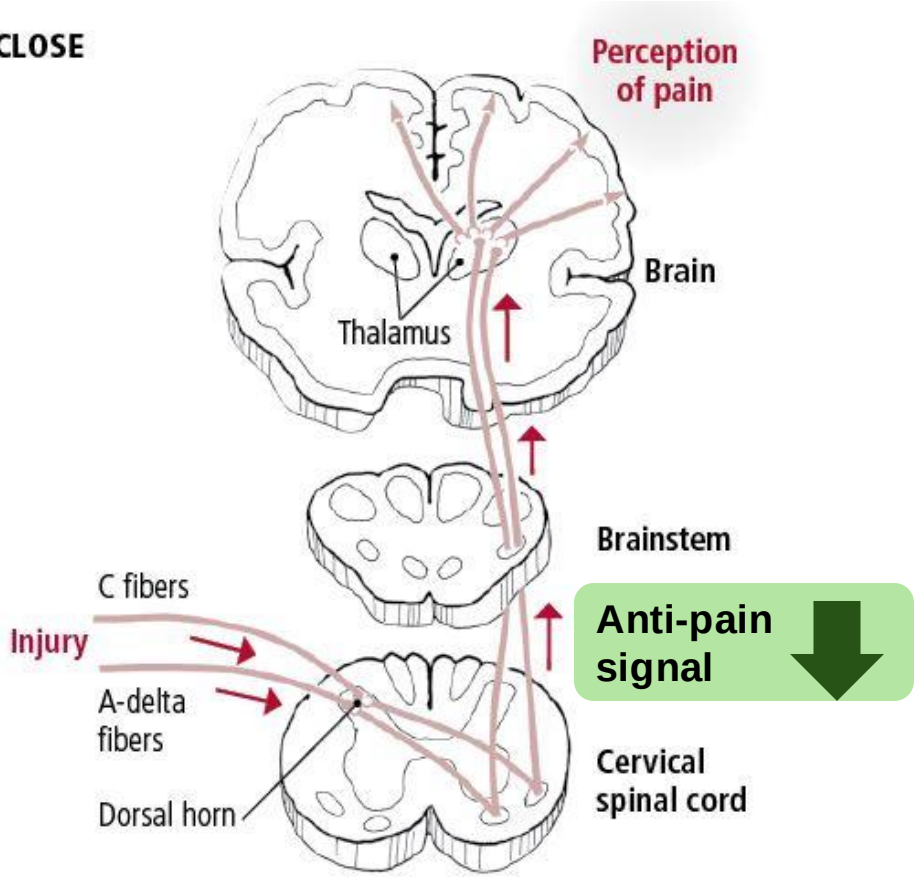
Neuromodulation Devices: Nerivio

How does Nerivio work?

Neuromodulation Devices: Nerivio

- **Mechanism**
  - Remote electrical neuromodulation (REN)
    - Stimulates the brainstem's descending inhibitory pain pathway → producing an **anti-pain signal** that improves headache and inducing **conditioned pain modulation**





Case: Jane

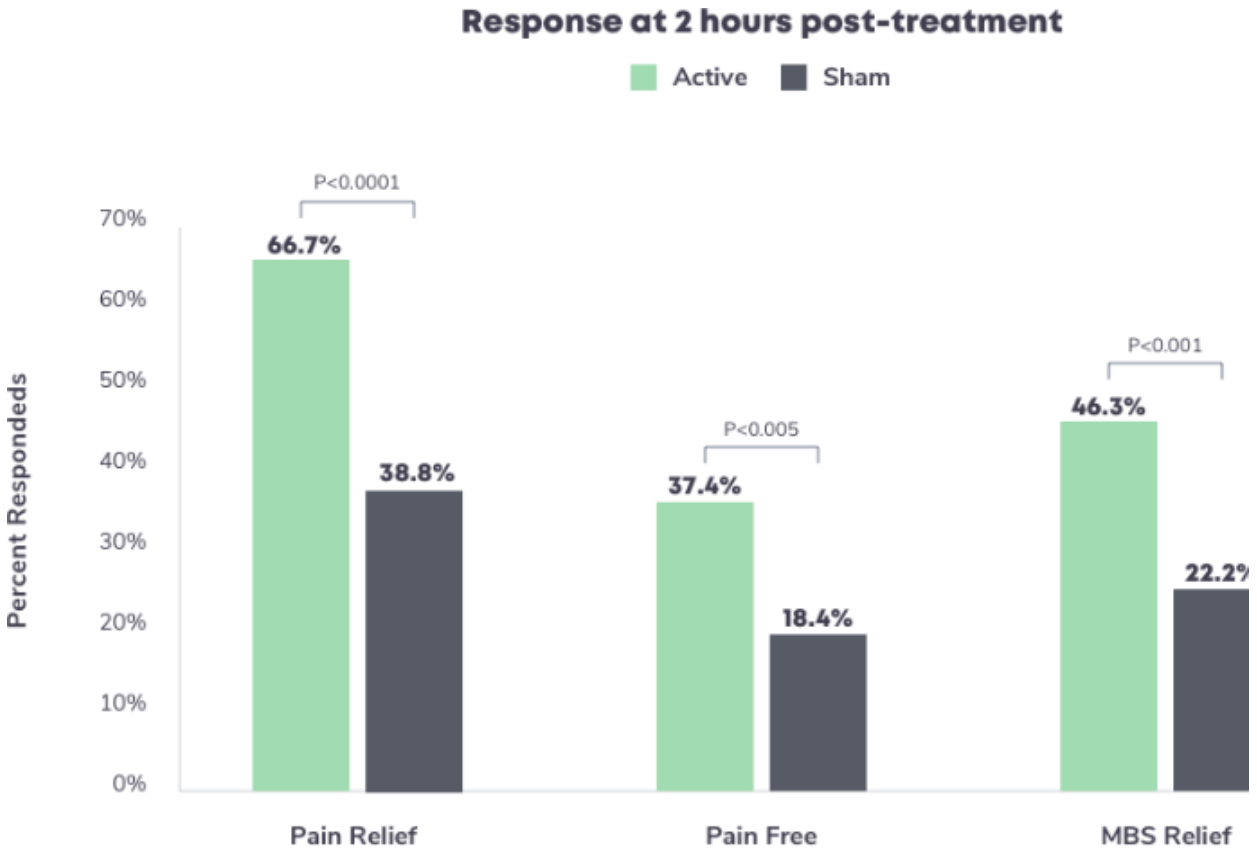
- Jane recently obtained her PhD, and she asks, “What supporting studies exist for this device?”

Neuromodulation Devices: Nerivio

What are the supporting studies?

Neuromodulation Devices: Nerivio

- **Four clinical trials**
  - Prospective, randomized, double-blind, sham-controlled, multicenter study in Israel and US
  - n=252 adults (18-75 years old)
  - Patients received the verum or sham stimulation
  - **Results:**
    - 2 hr pain relief **: 66.7% device** vs 38.8% sham
    - 2 hr pain freedom: **37.4% device** vs 18.4% sham



Reference: Yarnitsky D, Volokh L, Ironi A, et al. Nonpainful remote electrical stimulation alleviates episodic migraine pain. Neurology. 2017;88:1250-1255.

Case: Jane

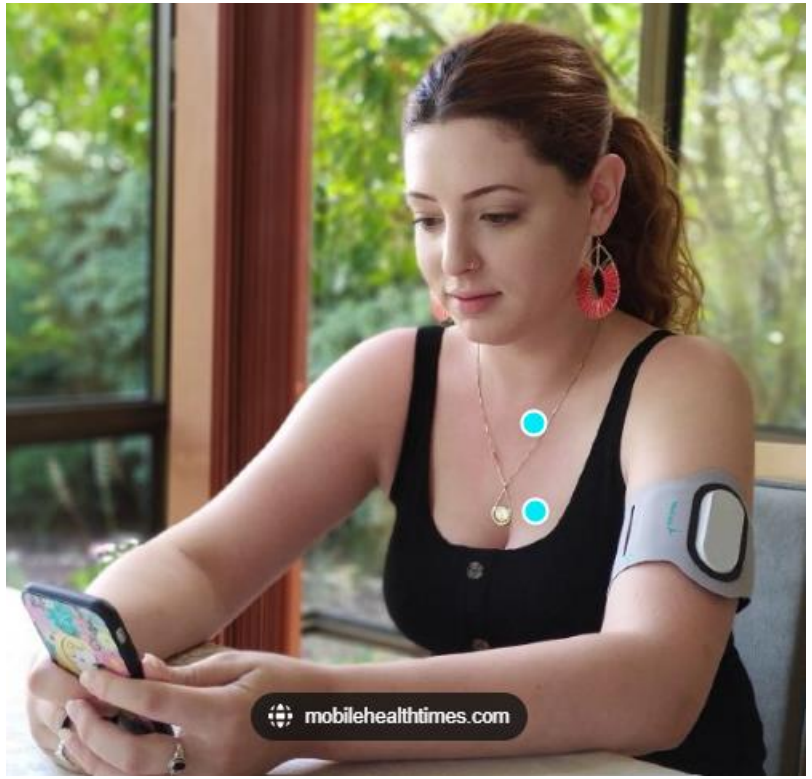
- Jane wonders what are the longer-term benefits of Nerivio?

Neuromodulation Devices: Nerivio

What are the longer term benefits of Nerivio?

Neuromodulation Devices: Nerivio

- **Four clinical trials**
  - 8-week open-label extension study: **Significant decrease in "usual care" acute medication usage**
  - **Minimal adverse events** (most common was 1.6% of patients with sensation of warmth on arm)
  - **Efficacy equivalent to triptans**
  - **Efficacy superior to NSAIDs**



Case: Jane

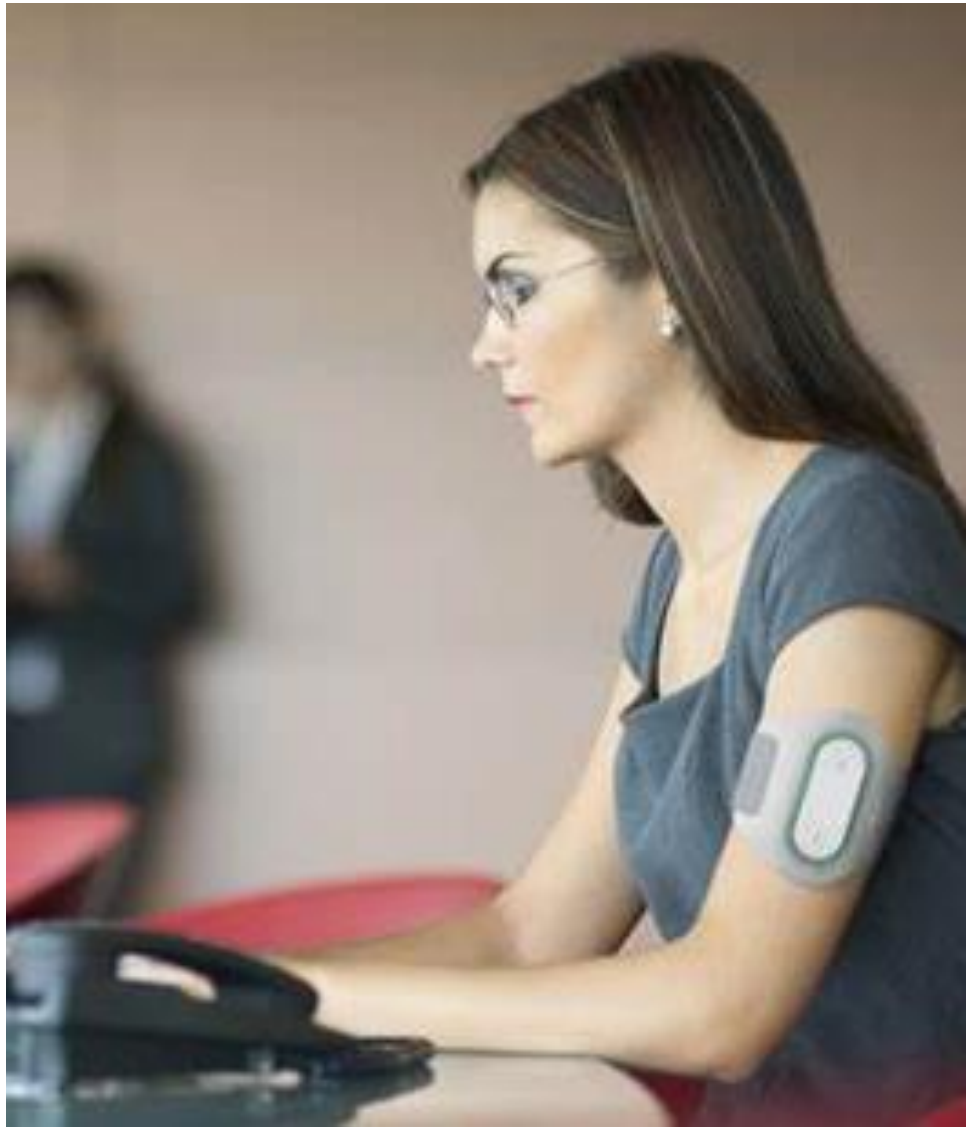
- Jane says, “Can I use this device for both acute and preventive treatment of migraine? Or just one of those?”

Neuromodulation Devices: Nerivio

Is Nerivio an acute or preventive treatment?

Neuromodulation Devices: Nerivio

- **Acute treatment:** 45-minute session as needed
- **Preventive treatment:** 45-minute session every other day



Case: Jane

- Jane asks, “What does the device feel like on the arm?”

Neuromodulation Devices: Nerivio

- With each use, **Nerivio intensity should feel strong but comfortable.**

- The intensity can be adjusted in the app (adjust by 1-2% increments). In clinical trials, intensities <20% were less effective.

- Adverse effects:
  - Warm, tingling sensation on arm (1.6%)
  - Tingling, numbness, or redness on skin (should disappear shortly after ending treatment)

Case: Jane

- Jane asks, “Am I a candidate for Nerivio?”

Neuromodulation Devices: Nerivio

For which patients should I consider Nerivio?

Neuromodulation Devices: Nerivio

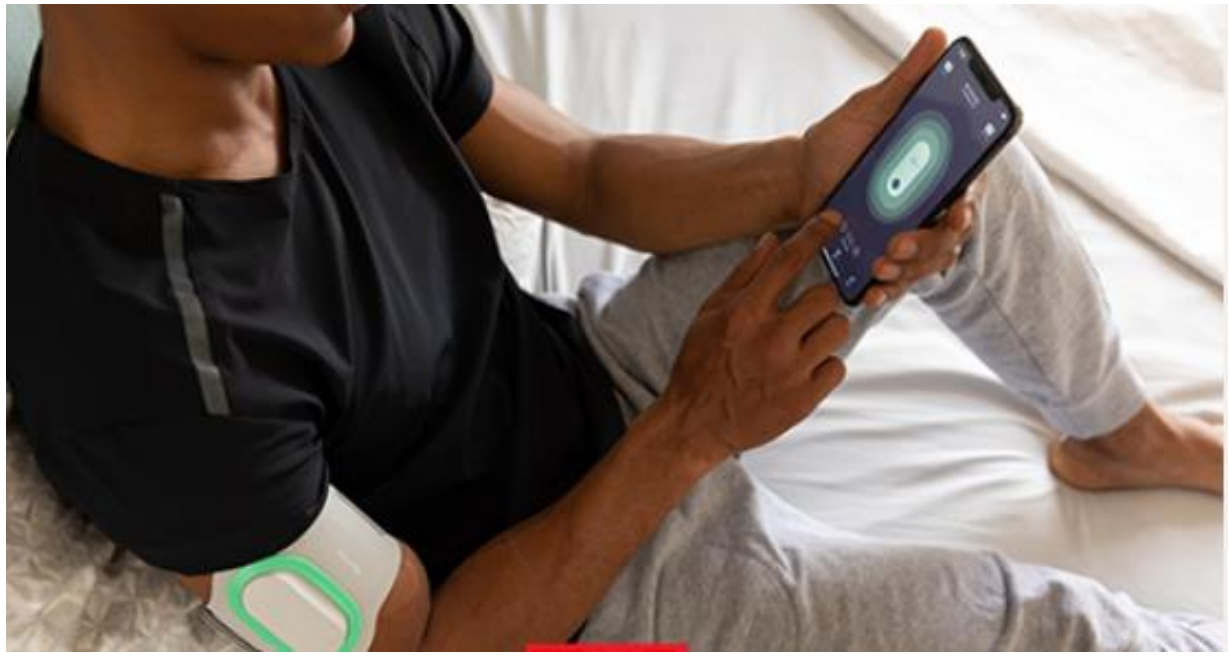
- **Almost everyone!**
- Patients who are looking to **bolster their acute and preventive approaches** for treatment of migraine
- Patients **at risk for medication overuse** headache (due to headache or other body pain)
- Patients who **prefer not to use medications**/injections
- Patients with **medical conditions** preventing them from taking traditional medications for headache
- Patients who have **limited access/interest in acute care services** for severe headache
- **≥ 12 years old** ★
- Those who **prefer not to have device on head (e.g., work/social)** ★

Neuromodulation Devices: Nerivio

What are the contraindications for Nerivio?

Neuromodulation Devices: Nerivio

- Congestive heart failure
- Severe cardiac or cerebrovascular disease
- Uncontrolled epilepsy
- Those with implantable medical device (e.g., pacemaker, hearing aid implant)



Neuromodulation Devices: Nerivio

What are the warnings prior to starting Nerivio?

Neuromodulation Devices: Nerivio

- Only use device on arm (no other body parts)
- Do not use device over skin conditions (e.g., open wounds, rashes)
- Do not use the device on an arm with a metallic implant (use it on the other arm)
- Do not use the device on wet skin

Case: Jane

- Jane states she is currently trying to get pregnant.
- She asks, “Can I use Nerivio in pregnancy?”

Neuromodulation Devices: Nerivio

Has Nerivio been studied in pregnancy?

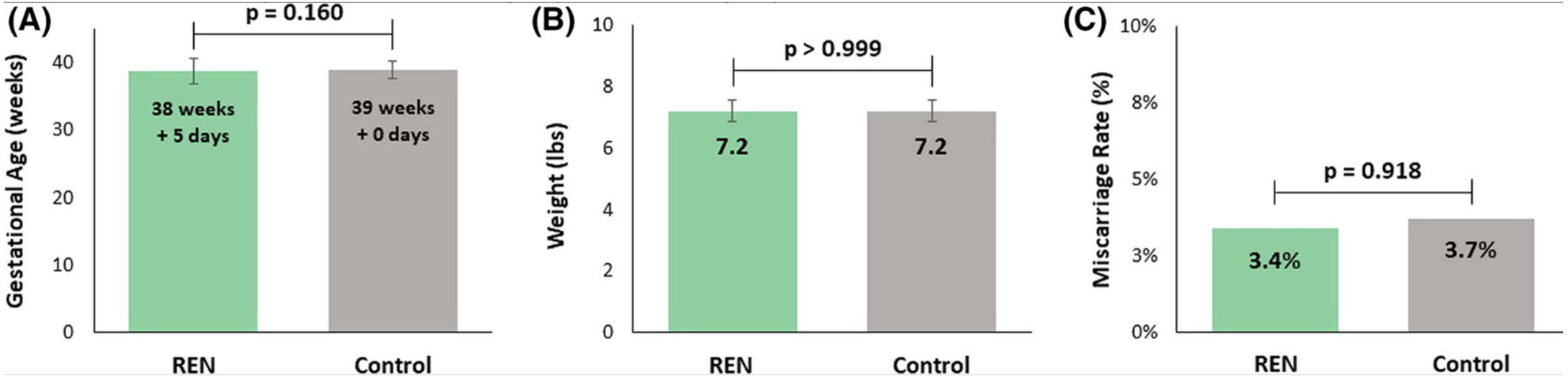
Neuromodulation Devices: Nerivio

- Retrospective study
- N = 140
- Conclusion: The REN device is **a safe treatment of migraine during pregnancy**, not increasing the risk for adverse pregnancy outcomes, and therefore offering a much-needed non-pharmacological alternative for women with migraine during pregnancy.

Safety of remote electrical neuromodulation for acute migraine treatment in pregnant women: A retrospective controlled survey-study

Addie Peretz MD, Alit Stark-Inbar PhD, Dagan Harris PhD, Shira Tamir MSc, Sharon Shmuely MSc, Alon Ironi MSEE, Audrey Halpern MD, Linus Chuang MD, Nina Riggins MD, PhD

First published: 19 June 2023 | https://doi.org/10.1111/head.14586 | Citations: 1



Case: Jane

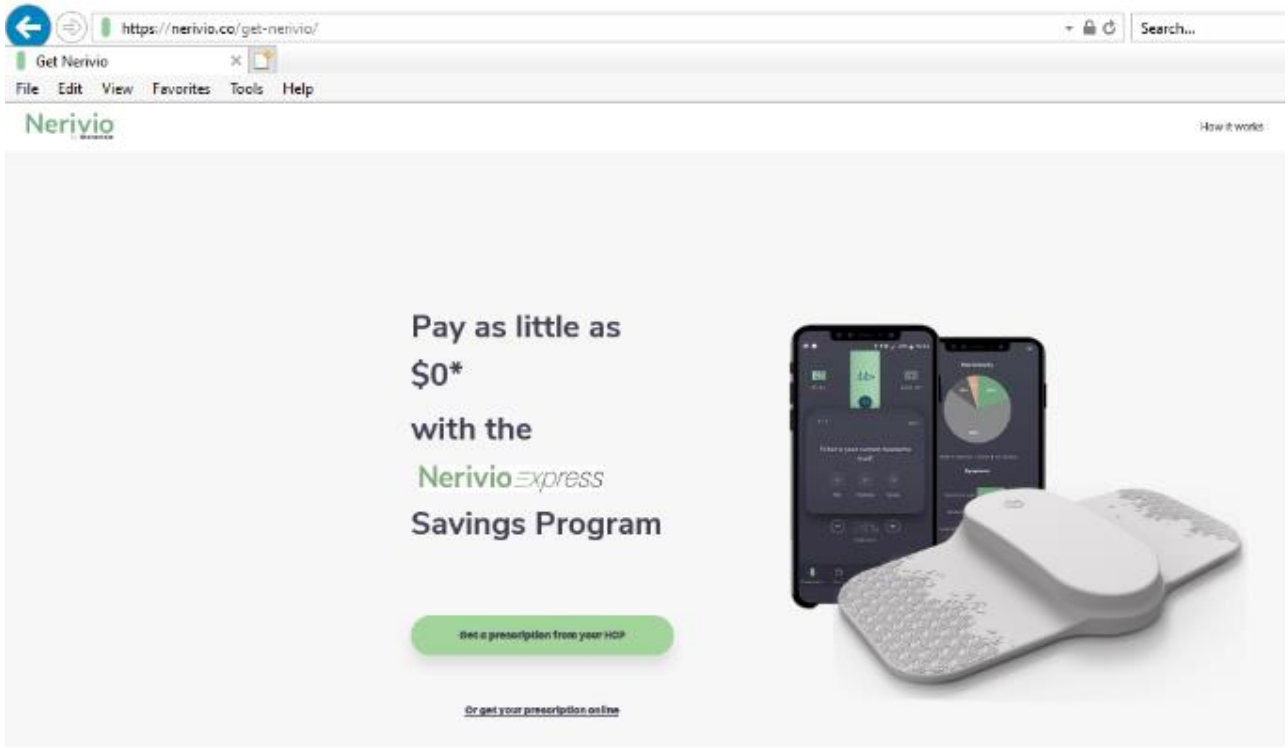
- Jane states she would like to start Nerivio.

Neuromodulation Devices: Nerivio

How can I get Nerivio for my patient?

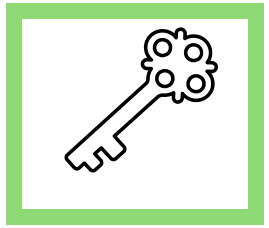
Neuromodulation Devices: Nerivio

- The patient can learn more about the device on the website, Nerivio.com
- The device can be prescribed through EPIC.
- Please assign the pharmacy to Procare Pharmacy in Miramar, FL
- Each device has the ability to treat 18 sessions
- Cost:
  - Free for military, BlueShield/Blue Cross
  - Otherwise, approx. $50 per devce



Neuromodulation Devices: Overview

- **Use as stand-alone or add-on treatment for migraine**
  - Stimulate the nervous system centrally or peripherally with an electric current
  - FDA-cleared for migraine



CEFALY

- Age ≥ 18
- Acute and preventive treatment
- Mechanism:
  - External trigeminal nerve stimulation
- AEs: Paresthesia, sleepiness

Nerivio

- Age ≥ 12
- Acute and preventive treatment
- Mechanism:
  - Remote electrical neuromodulation affecting desc. inhibitory pain pathways
- AEs: Paresthesia, warmth at site of skin

GammaCore

- Age ≥ 12
- Acute and preventive treatment
- Mechanism:
  - Vagus nerve stimulation
- AE: Discomfort at site of skin

Relivion

- Age ≥ 18
- Acute treatment
- Mechanism:
  - Stimulates trigeminal and occipital nerves
- AEs: Migraine, pain, paresthesia at site of skin

Neuromodulation Devices: Decision-making

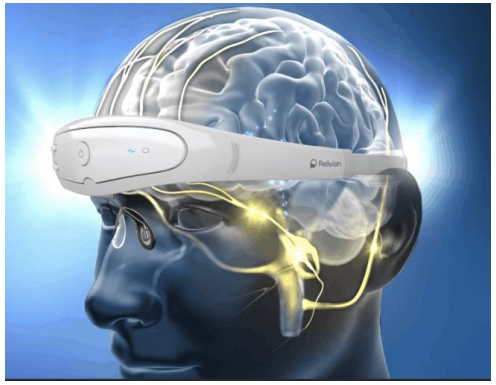
How do I know which device is best for my patient?

Neuromodulation Devices: Decision-making

- Much of the decision-making comes down to:
  - COST
  - Headache frequency
  - We often start with CEFALY, which has a 3 month return policy – money back guarantee
  - Some patients require two neuromodulation devices (e.g., use Cefaly and Nerivio intermittently)

CEFALY

Nerivio



Relivion

GammaCore

Neuromodulation Devices: Summary

- Find out from your patients how many headache days they are having per month. **If 4 or more headache days per month, consider neuromodulation for prevention.**

- **Consider neuromodulation for acute treatment in all patients!** Please do not routinely recommend Tylenol, ibuprofen, etc., use of more than 4 days per month total, as this can worsen headache/chronic pain. Neuromodulation is a better alternative.