CEFALY TECHNOLOGY

19 Old Kings Highway South
Suite 200
Darien, CT 06820

1.844.475.7100

CEFALY SCIENTIFIC COMPENDIUM

Summaries of Clinical Studies for external Trigeminal Nerve Stimulation for Migraine

CEFALY TECHNOLOGY

19 Old Kings Highway South
Suite 200
Darien, CT 06820
1.844.475.7100

Background:

The CEFALY external Trigeminal Nerve Stimulation (e-TNS) device is indicated for the acute treatment of migraine with or without aura in patients 18 years of age or older and the prophylactic treatment of episodic migraine in patients 18 years of age or older. This Scientific Compendium is an educational resource summarizing the clinical studies of e-TNS for the treatment of migraine headache.

The efficacy and safety of migraine prevention with the CEFALY device was established in the prospective, randomized, sham-controlled clinical trial "PREMICE" (Migraine prevention with a supraorbital transcutaneous stimulator: a randomized controlled trial).

With daily 20-minute e-TNS treatment patients with migraine experience:

- Significant reduction in the number of monthly migraine attacks[1]
- Significant reduction in the number of monthly headache days[1]
- Significant reduction in acute medication intake[1]

The efficacy and safety of acute treatment for migraine attacks was demonstrated in the prospective, randomized, sham-controlled clinical trial "ACME" (Acute migraine therapy with external trigeminal neurostimulation: A randomized controlled trial).

With 60-minute e-TNS treatment for acute migraine attacks:

- Reduction in migraine severity at 2 hours sustained over 24 hours[2]
- Some patients experience pain freedom at 2-hours post treatment[2]

Below you will find a summary of the peer-reviewed published clinical data demonstrating efficacy and safety of e-TNS therapy for the acute and preventative treatment of migraine headaches.

1. Schoenen, J., Vandersmissen, B., Jeangette, S., Herroelen, L., Vandenheede, M., Gérard, P., & Magis, D. (2013). Migraine prevention with a supraorbital transcutaneous stimulator: a randomized controlled trial. *Neurology*, *80*(8), 697-704.
2. Chou, D. E., Shnayderman Yugrakh, M., Winegarner, D., Rowe, V., Kuruvilla, D., & Schoenen, J. (2019). Acute migraine therapy with external trigeminal neurostimulation (ACME): A randomized controlled trial. *Cephalalgia*, *39*(1), 3-14.

19 Old Kings Highway South
Suite 200
Darien, CT 06820
1.844.475.7100

TABLE OF CONTENTS

CEFALY TECHNOLOGY

19 Old Kings Highway South
Suite 200
Darien, CT 06820
1.844.475.7100

MIGRAINE PREVENTION WITH SUPRAORBITAL TRANSCUTANEOUS STIMULATOR: A RANDOMIZED CONTROLLED TRIAL

Schoenen J. Vandersmissen B. Jeangette S. Herroelen L. Vandenheede M. Géard P. Magis D. *Neurology*. 201: 80(8):697-704

OBJECTIVE:

The assess the efficacy and safety of external trigeminal nerve stimulation with the CEFALY supraorbital transcutaneous stimulator in migraine prevention

STUDY TYPE: Prospective, double-blinded, randomized, sham-controlled trail conducted at 5 Belgian tertiary headache clinics.

STUDY DESIGN: Sixty-seven (67) adult patients (age 18-65), with at least 2 migraines with or without aura per month, were randomized to receive 20-minute daily e-TNS verum stimulation (n=34) or sham stimulation (n=33). The primary outcome measures included the percentage of migraine responders or patients with a 50% reduction of monthly migraine days. Secondary outcome measures included (1) change in monthly migraine attack frequency, (2) change in monthly headache frequency (3) change in monthly acute migraine drug use compared to run-in and (4) percentage of patients satisfied with the treatment at the end of the 3-month period.

RESULTS:

Primary

- *Migraine responders*: At the end of the 3rd month, 26% more patients in the verum stimulation group experienced a reduction of migraine frequency by 50% compared to the sham (38.24-verum, 12.12 sham, p=0.023)

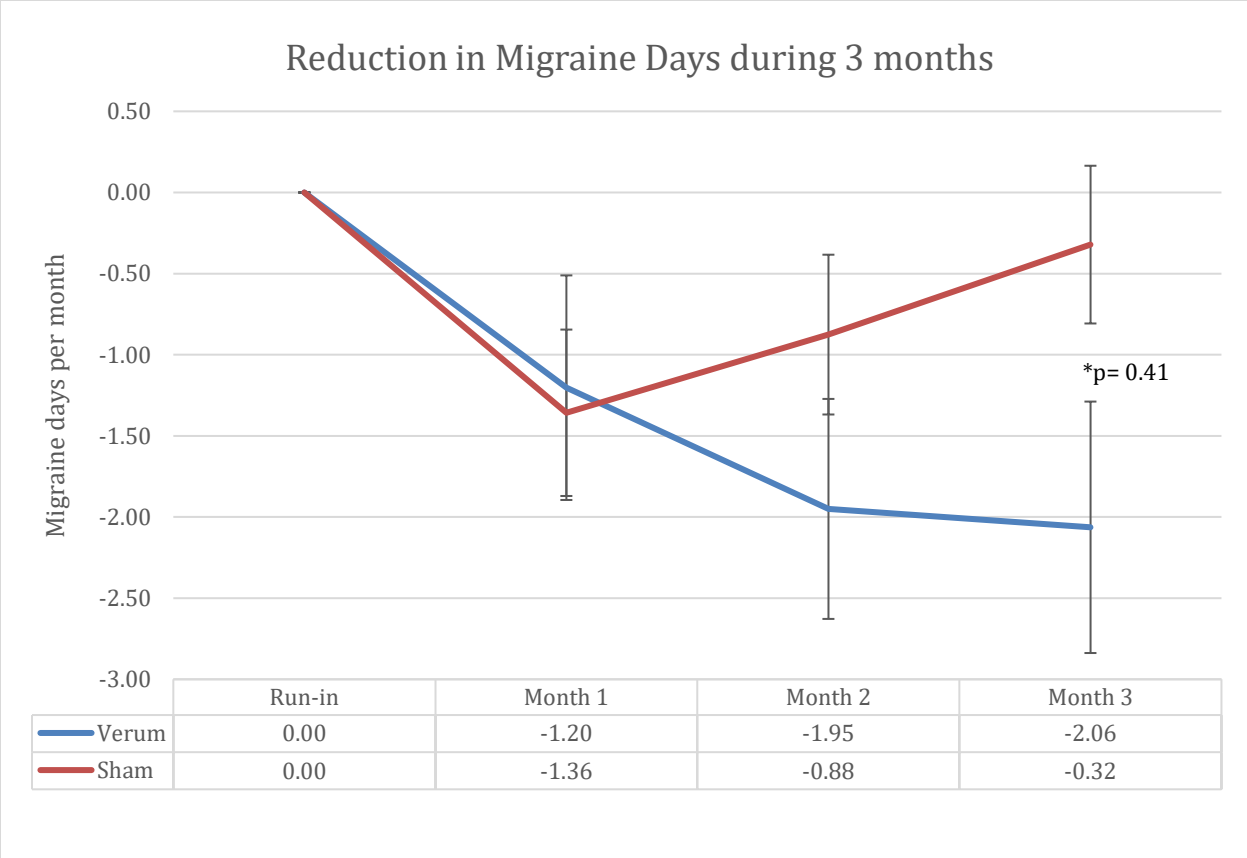
Secondary

- *Migraine attacks*: Verum e-TNS stimulation resulted in a 15.5% therapeutic reduction in monthly migraine attacks compared to sham stimulation (19% reduction-verum, 3.5% reduction-sham, p=0.044)

CEFALY TECHNOLOGY

19 Old Kings Highway South
Suite 200
Darien, CT 06820
1.844.475.7100

- *Headache days*: Verum e-TNS stimulation resulted in a 29% therapeutic reduction in monthly (any) headache days compare to sham stimulation (33% reduction-verum, 4.1% reduction-sham, p=0.041)
- *Monthly acute migraine medication intake*: Verum e-TNS stimulation provided a 36% therapeutic reduction in monthly acute anti-migraine medication intake over the 3-month period compared to sham stimulation (36.64% reduction-verum, 0.46% reduction-sham, p= 0.0072)
- *Monthly acute migraine medication & Migraine responders:* Among verum stimulation patients reporting a 50% reduction of migraine frequency at the 3-month period, e-TNS resulted in a 74% therapeutic reduction in monthly acute anti-migraine therapy compared to the sham stimulation group (74.5% reduction verum, 0.46% reduction-sham, p=0.0017)
- *Satisfaction with therapy*: 70% of verum e-TNS group were very, or moderately, satisfied with the treatment compared with 39.4% in the sham stimulation group.



	Run-in	Month 1	Month 2	Month 3
Verum	0.00	-1.20	-1.95	-2.06
Sham	0.00	-1.36	-0.88	-0.32

*Figure 1: Reduction of Migraine Days during 3-month period of 20-minute PREVENT treatment with e-TNS. * The reduction in migraine days was significantly lower in the verum group compared to placebo at 3 months.*

19 Old Kings Highway South
Suite 200
Darien, CT 06820
1.844.475.7100

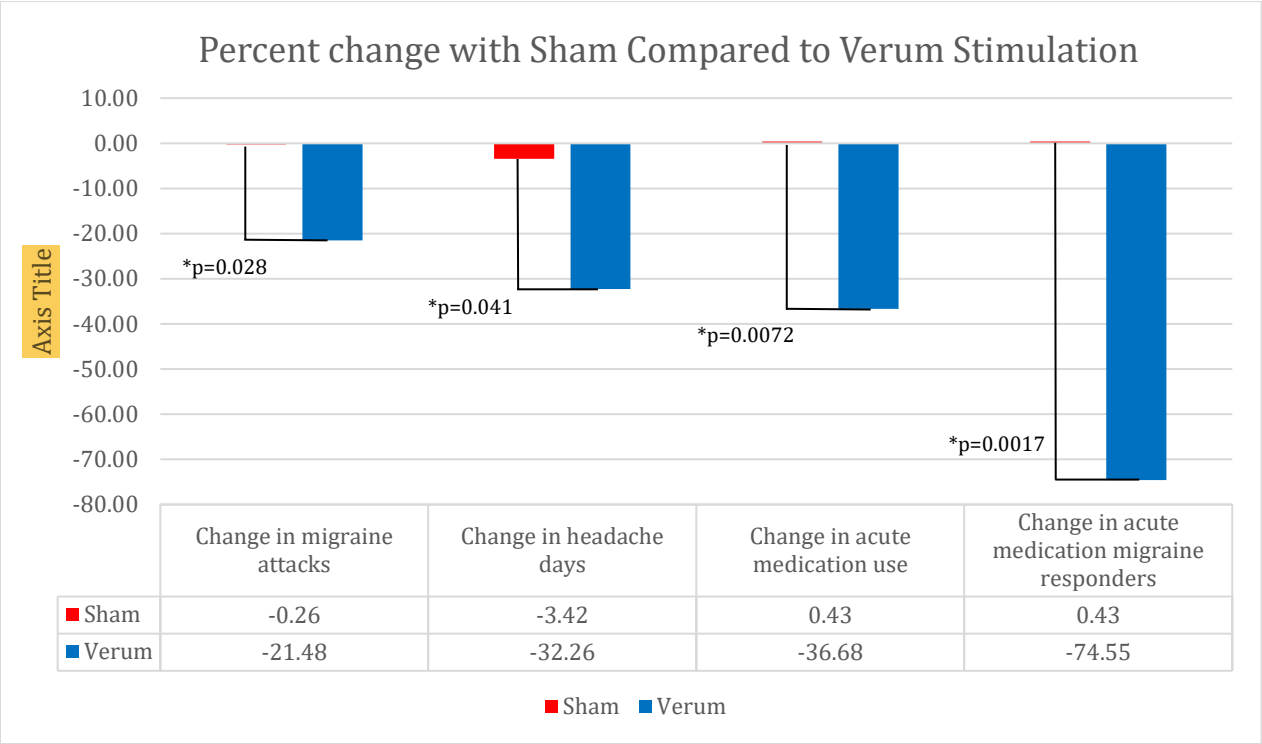


Figure 2: CEFALY PREVENT users experienced a significant reduction in the number of migraine attacks, reduction of headache days and acute monthly medication use.

SAFETY AND COMPLIANCE:

- There were no reported adverse events or side effects reported in either the verum or sham groups
- Overall compliance with daily treatment sessions reached 61.7% between both groups (patients used the treatment device just over 60% of the intended time for 3 months)

KEY CONCLUSIONS

- Daily 20-minute, e-TNS therapy significantly reduced the frequency of monthly migraine attacks, monthly headache days and acute migraine medication intake over 3 months
- E-TNS therapy was well tolerated in patients with migraine headaches without serious adverse events
- Patients receiving e-TNS therapy expressed satisfaction with therapy

CEFALY TECHNOLOGY

19 Old Kings Highway South
Suite 200
Darien, CT 06820
1.844.475.7100

ACUTE MIGRAINE THERAPY WITH EXTERNAL TRIGEMINAL NEUROSTIMULATION (ACME): A RANDOMIZED CONTROLLED TRIAL

Chou D. Yugrakh M. Winegarner D. Rowe V. Kuruvilla D. Schoenen J. Cephalagia. 2019. 39(1), 3-14

OBJECTIVE:

To assess the safety and efficacy of 1-hour external trigeminal nerve stimulation (e-TNS) for acute treatment of migraine attacks.

STUDY TYPE: Prospective, double-blind, randomized, sham-controlled clinical trial conducted in three headache centers in the United States.

STUDY DESIGN: One hundred and six (106) patients with acute migraine attack lasting at least 3 hours were randomized to receive 1-hour verum e-TNS stimulation (n=52) or sham stimulation (n=54). Patients were not permitted to take acute migraine medication prior to e-TNS verum or sham stimulation. The primary outcome was the mean change in migraine pain at 1-hour compared to baseline as measured by the visual analogue scale (VAS). Secondary outcome measures included (1) mean change in VAS pain score at the 2 and 24-hour point compared to baseline, (2) pain freedom at 1 hour and (3) the percentage of migraine responders or patients with ≥pain relief at 1 hour.

RESULTS:

Primary

- The verum e-TNS stimulation resulted in a 29% therapeutic reduction in average migraine severity after 1 hour of treatment compared to sham stimulation group (59% reduction-verum, 30% reduction-sham, p<0.0001

Secondary

- The verum e-TNS stimulation was associated with sustained migraine relief at 2- and 24-hour after treatment resulting in a 18% and 17% therapeutic reduction in VAS compared to sham stimulation respectively (2-hour: 50%-verum, 32% sham, p=0.026; 24-hour: 57%-verum, 40%-sham, p=0.0.37)
- At 1 hour, 22% more patients in the verum e-TNS stimulation group experienced pain freedom compared to sham stimulation group (15-verum, 3-sham, p=0.0016)

19 Old Kings Highway South
Suite 200
Darien, CT 06820
1.844.475.7100

- At 1-hour post-treatment, 32% more patients who received verum e-TNS stimulation were migraine responders or experienced a reduction of migraine severity by 50% (33-verum, 17-sham, p=0.0017)

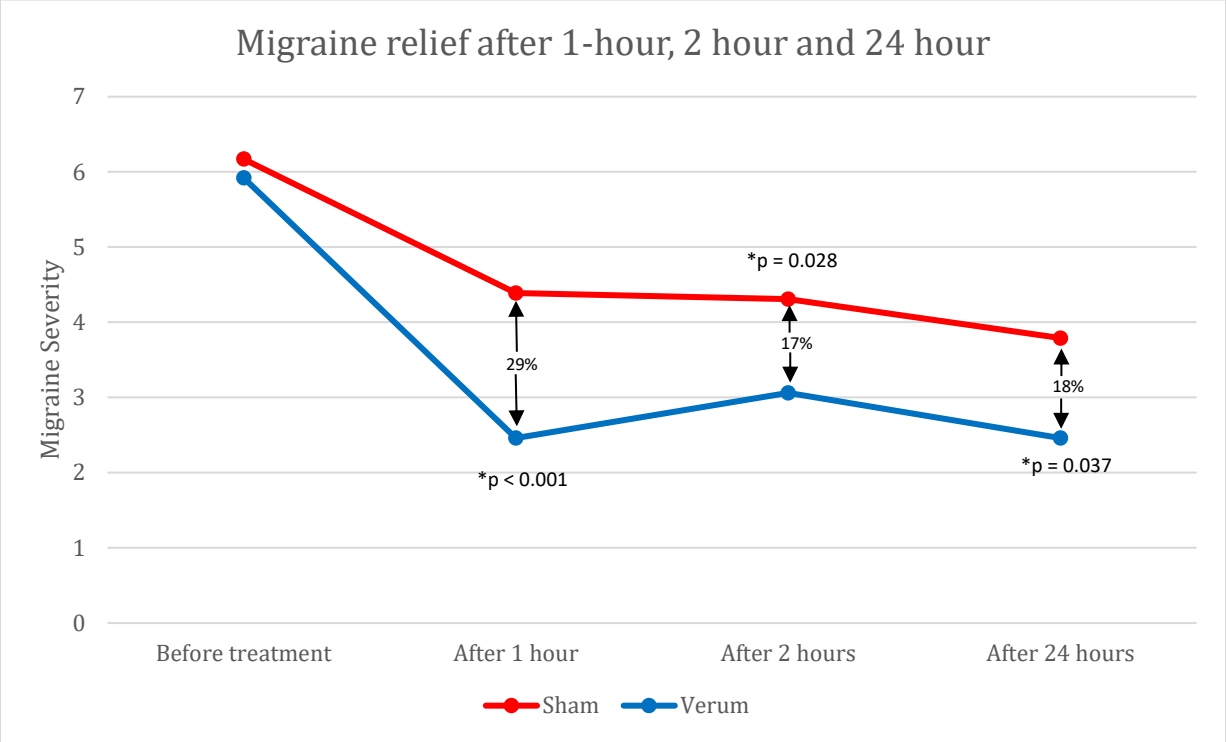


*Figure 3: CEFALY Acute users experienced sustained migraine relief up to 2 -hours after 60-minute treatment. * Specifically, 60-minute verum stimulation demonstrates significant reduction in migraine severity after 1, 2, and 24-hours compared to sham.*

SAFETY AND COMPLIANCE:

- No serious adverse events or adverse device effects reported during the study
- Three patients (2-verum, 1-sham) were unable to tolerate paresthesia sensation at 5 minutes and were randomized in the study.
- Four patients (3-verum, 1-sham) discontinued treatment before the end of the 1-hour session
    - 2 (verum) withdrew due to inability to tolerate treatment stimulation intensity
    - 1 (verum) withdrew due to nausea during treatment session
- All minor adverse events were temporary with full recovery within 24 hours

CEFALY TECHNOLOGY

19 Old Kings Highway South
Suite 200
Darien, CT 06820

1.844.475.7100

KEY CONCLUSIONS

- External Trigeminal Nerve (e-TNS) stimulation is a safe and effective acute treatment for migraine attacks
- The efficacy of acute treatment with e-TNS for migraine attack is sustained for 24-hours.
- There are no serious adverse effects associated with e-TNS and all minor adverse events were fully reversible within 24 hours of the intervention

19 Old Kings Highway South
Suite 200
Darien, CT 06820
1.844.475.7100

PHASE 3 RANDOMIZED, DOUBLE-BLIND, SHAM-CONTROLLED TRIAL OF E-TNS FOR THE ACUTE TREATMENT OF MIGRAINE (TEAM)

Kuruvilla DE. Mann JI. Tepper SJ. Starling AJ. Panza G. Johnson MAL. *Manuscript Pending Review.*

OBJECTIVE:

To assess the safety and efficacy of consecutive 2-hour external trigeminal nerve stimulation (e-TNS) for acute treatment of migraine attacks in the out of hospital setting.

STUDY TYPE: Prospective, double-blind, randomized, sham-controlled clinical trial conducted in ten headache centers in the United States.

STUDY DESIGN: Five hundred thirty-eight (538) patients with acute moderate-to-severe intensity migraine attack were randomized to receive consecutive 2-hour verum e-TNS stimulation (n=259) or sham stimulation (n=279). Patients were not permitted to take acute migraine medication prior to e-TNS verum or sham stimulation. The primary outcomes included (1) pain freedom at 2 hours and (2) resolution of most bothersome migraine-associated symptom. Secondary outcomes include (1) pain relief at 2 hours, (2) absence of all migraine associated symptoms and (3) sustained pain freedom at 2 and 24 hours.

RESULTS:

Primary

- Consecutive 2-hour verum e-TNS resulted in 7.2% higher rates of pain freedom at 2 hours compared to sham stimulation (25.5% -verum, 18.3%- sham, p <0.043)
- Verum 2-hour e-TNS stimulation resulted in a 14.1% therapeutic reduction most bothersome migraine associated symptom (56.4% - verum, 42.3%- sham, p < 0.001).

Secondary

- At 2 hours, verum e-TNS was associated with a 14.3% therapeutic reduction in migraine pain severity compared to sham stimulation (69.5% – verum, 55.2% -sham, p <0.001)
- Absence of migraine associated symptoms at 2 hours were significantly 8.4% higher in the verum e-TNS group compared to sham stimulation (42.5%-verum, 34.1%-sham, p <0.044)
- Sustained pain freedom and pain relief 24-hour was 7% and 11.5% higher, respectively, the in verum e-TNS group compared to sham (pain freedom: 22.8%-verum, 15.8%-sham, p=0.039. pain relief: 45.9%- verum, 34.4%- sham, p= 0.006)

19 Old Kings Highway South
Suite 200
Darien, CT 06820
1.844.475.7100

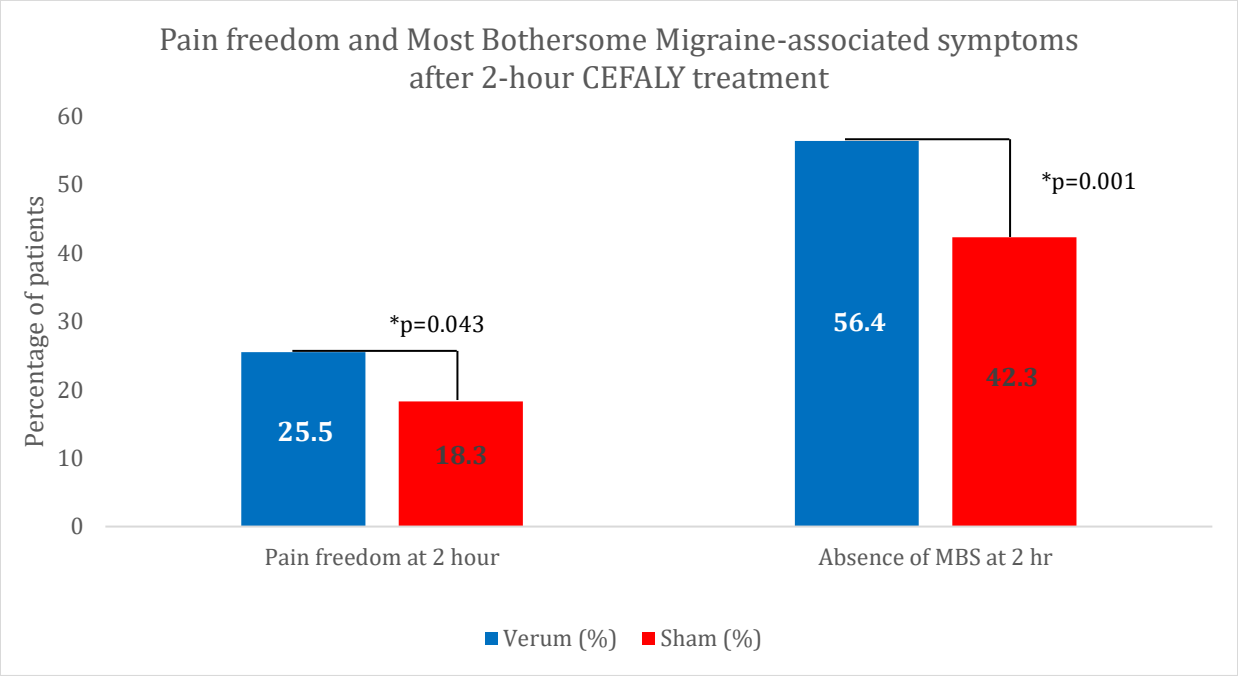


Figure 4: Two-hour CEFALY treatment was associated with 7.2% higher rate of pain freedom at 2 hours and 14.1% higher rate of resolution of most bothersome migraine associated symptom.

SAFETY AND COMPLIANCE:

- No serious adverse effects were encountered in the study
- The adverse event rate in the verum group was 5.6% higher than the sham with the predominant difference in the rate of stimulation related forehead paresthesia and discomfort (3.5%-verum, 0.4%-sham, p =0.009).
- All adverse effects were minor and fully reversible without intervention or additional treatment.

CEFALY TECHNOLOGY

19 Old Kings Highway South
Suite 200
Darien, CT 06820

1.844.475.7100

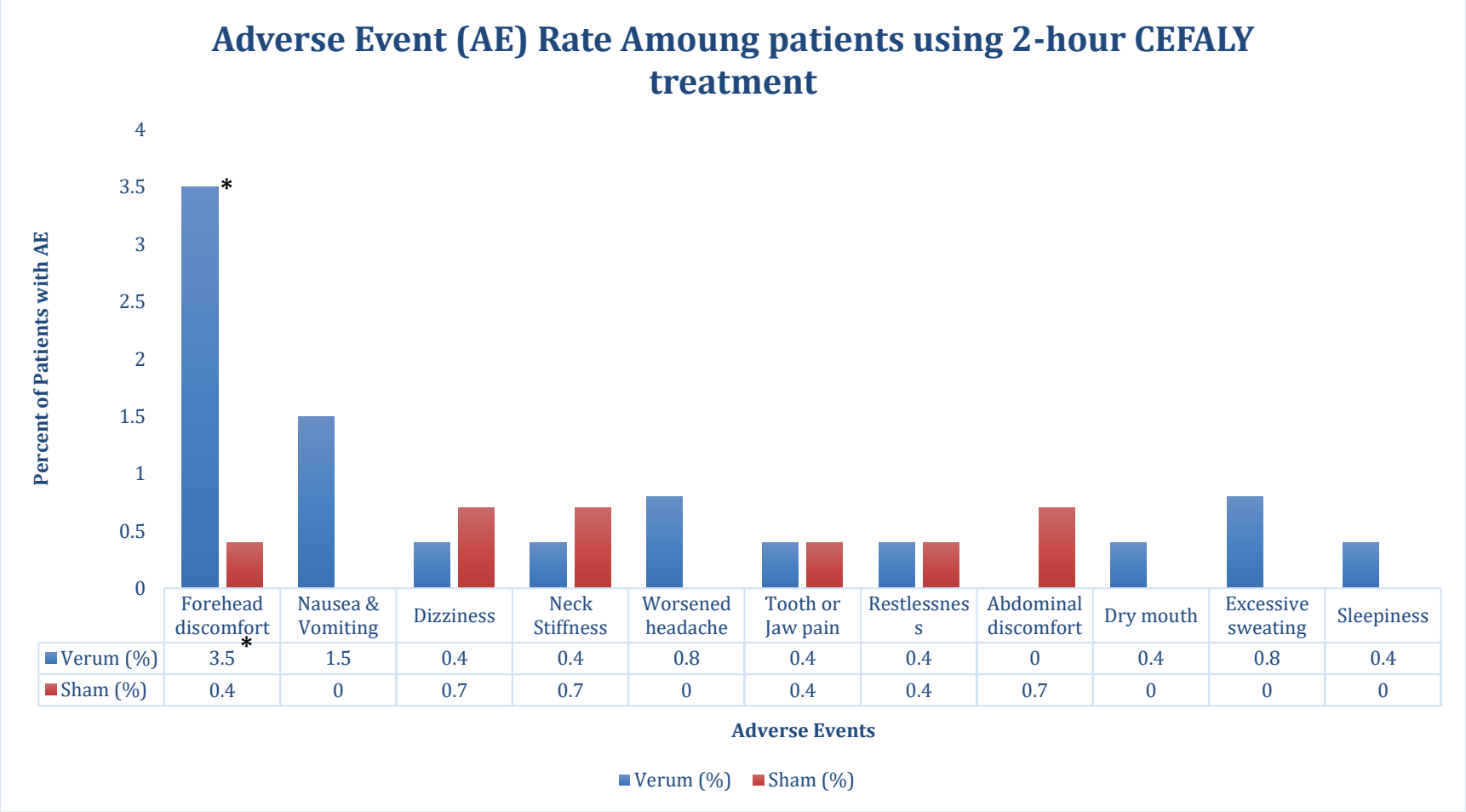


*Figure 5: Adverse Events comparing verum stimulation (blue) and sham stimulation (red). Overall, the rate of adverse events was similar among groups except for stimulation related forehead discomfort which was 3.1% higher in patients in the verum stimulation group (*p= 0.009).*

CEFALY TECHNOLOGY

19 Old Kings Highway South
Suite 200
Darien, CT 06820

1.844.475.7100

KEY CONCLUSIONS

- Two-hour External Trigeminal Nerve (e-TNS) stimulation is a safe and effective non-invasive treatment for migraine attacks in the at-home setting
- Two-hour e-TNS therapy for acute migraine attacks was associated with resolution of migraine-associated most bothersome symptom.

CEFALY TECHNOLOGY

19 Old Kings Highway South
Suite 200
Darien, CT 06820

1.844.475.7100

Selected Articles About e-TNS Therapy:

Schoenen, J., Vandersmissen, B., Jeangette, S., Herroelen, L., Vandenheede, M., Gérard, P., & Magis, D. (2013). Migraine prevention with a supraorbital transcutaneous stimulator: a randomized controlled trial. *Neurology*, *80*(8), 697-704.

Chou, D. E., Shnayderman Yugrakh, M., Winegarner, D., Rowe, V., Kuruvilla, D., & Schoenen, J. (2019). Acute migraine therapy with external trigeminal neurostimulation (ACME): A randomized controlled trial. *Cephalalgia*, *39*(1), 3-14.

Magis, D., D'Ostilio, K., Thibaut, A., De Pasqua, V., Gerard, P., Hustinx, R., ... & Schoenen, J. (2017). Cerebral metabolism before and after external trigeminal nerve stimulation in episodic migraine. *Cephalalgia*, 37(9), 881-891.

Magis, D., Sava, S., d'Elia, T. S., Baschi, R., & Schoenen, J. (2013). 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. *The journal of headache and pain*, 14(1), 1-8.

Ordás, C. M., Cuadrado, M. L., Pareja, J. A., de-Las-Casas-Cámara, G., Gómez-Vicente, L., Torres-Gaona, G., ... & Pardo-Moreno, J. (2020). Transcutaneous supraorbital stimulation as a preventive treatment for chronic migraine: a prospective, open-label study. *Pain Medicine*, 21(2), 415-422.

Di Fiore, P., Bussone, G., Galli, A., Didier, H., Peccarisi, C., D'Amico, D., & Frediani, F. (2017). Transcutaneous supraorbital neurostimulation for the prevention of chronic migraine: a prospective, open-label preliminary trial. *Neurological Sciences*, 38(S1), 201–206. doi:10.1007/s10072-017-2916-7

Piquet, M., Balestra, C., Sava, S. L., & Schoenen, J. E. (2011). Supraorbital transcutaneous neurostimulation has sedative effects in healthy subjects. *BMC Neurology*, 11(1). doi:10.1186/1471-2377-11-135