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Non-invasive Vagus Nerve Stimulation for Acute Treatment of Episodic and Chronic Cluster Headache: Pooled Analysis of Data From Two Randomised, Double-blind, Sham-Controlled Clinical Trials

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Aim of Research

- By pooling and analysing data from 2 large clinical trials, we aimed to provide a complete assessment of possible differential effects of non-invasive vagus nerve stimulation (nVNS) in the acute treatment of episodic and chronic cluster headache

Introduction

- There remains an unmet need for effective, tolerable, easy-to-use treatments for acute cluster headache attacks, particularly in patients with more than two attacks in 24 hours
- Efficacy and safety of nVNS in the acute treatment of cluster headache were investigated in two similar randomised, double-blind, sham-controlled clinical trials (ACT1[1] and ACT2[2])
  - Individually, these studies were underpowered for analysis of differential effects of nVNS in episodic and chronic cluster headache
- Data from ACT1 and ACT2 were pooled and analysed to gain more complete, clinically instructive insight into the use of nVNS as acute treatment for cluster headache attacks

Methods

- Data from all participants in ACT1 and ACT2 were pooled (**Table 1**)
- Identical active sham devices, which delivered perceptible stimuli but did not activate the vagus nerve, were used in both studies
- Efficacy was evaluated in the total pooled population and in the episodic and chronic subgroups individually
- Safety was evaluated in the total pooled population
- *Responder status* was defined as the proportion of patients with a score of 0 or 1 on a 5-point pain intensity scale in which 0=no pain and 4=very severe pain
- When rescue medication was used within 60 minutes (for ACT1) or at any point (for ACT2) after initiation of stimulation for an attack, that attack was considered a treatment failure

Table 1. ACT1 and ACT2 Highlights

Study Parameter	ACT1	ACT2
Size (full-analysis set)	*n*=133 (episodic, 85; chronic, 48)	*n*=92 (episodic, 27; chronic, 65)
Geography	20 US centres	9 UK and EU centres
Primary end point	Subject responder status, first attack	Pain-free attack status, all treated attacks
Cervical treatment	Right side	Ipsilateral to pain
Double-blind period	1 month (5 attacks)	2 weeks (all attacks)
Treatment regimen	3 stimulations/attack	3 (+3 as needed) stimulations/attack
Maximum No. of attacks treated per day	2	4

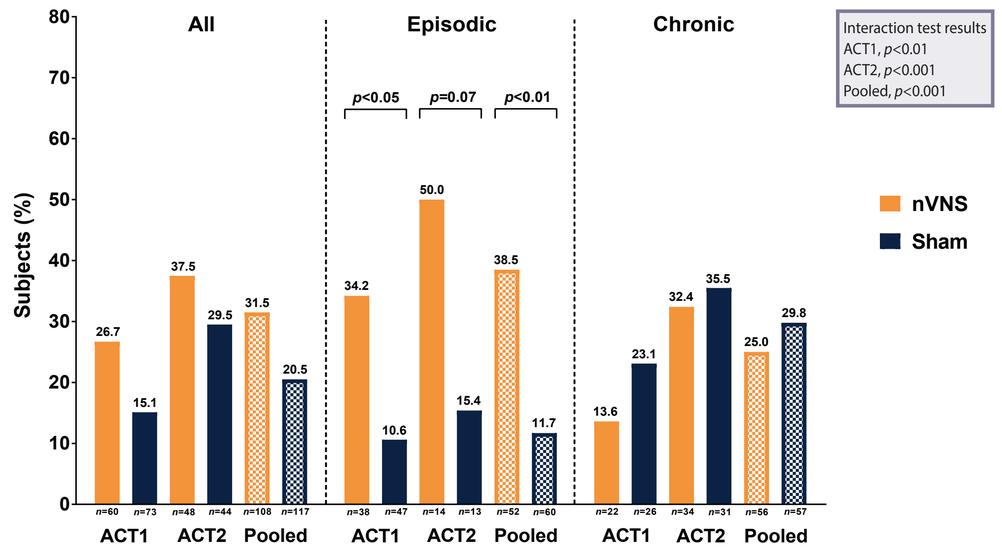
Results

Table 2. Demographic and Baseline Characteristics

Characteristic	By Treatment Group		By Subgroup	
	nVNS (*n*=124)	Sham (*n*=129)	Episodic (*n*=131)	Chronic (*n*=122)
Age, mean (SD), years	45.4 (12.4)[a]	47.8 (11.2)[b]	47.3 (12.4)[c]	45.9 (11.1)[d]
Male, No. (%)	94 (75.8)	105 (81.4)	106 (80.9)	93 (76.2)
Ethnic origin, No. (%)				
Asian	5 (4.0)	1 (0.8)	4 (3.1)	2 (1.6)
Black	5 (4.0)	7 (5.4)	9 (6.9)	3 (2.5)
White	113 (91.1)	120 (93.0)	117 (89.3)	116 (95.1)
Missing	1 (0.8)	1 (0.8)	1 (0.8)	1 (0.8)
Cluster headache type, No. (%)				
Episodic	65 (52.4)	66 (51.2)	131 (100.0)	0
Chronic	59 (47.6)	63 (48.8)	0	122 (100.0)
Treatments used to manage cluster headache, n/N (%)				
Acute	114/123 (92.7)	121/125 (96.8)	121/130 (93.1)	114/118 (96.6)
Preventive	75/123 (61.0)	92/125 (73.6)	83/130 (63.9)	84/118 (71.2)

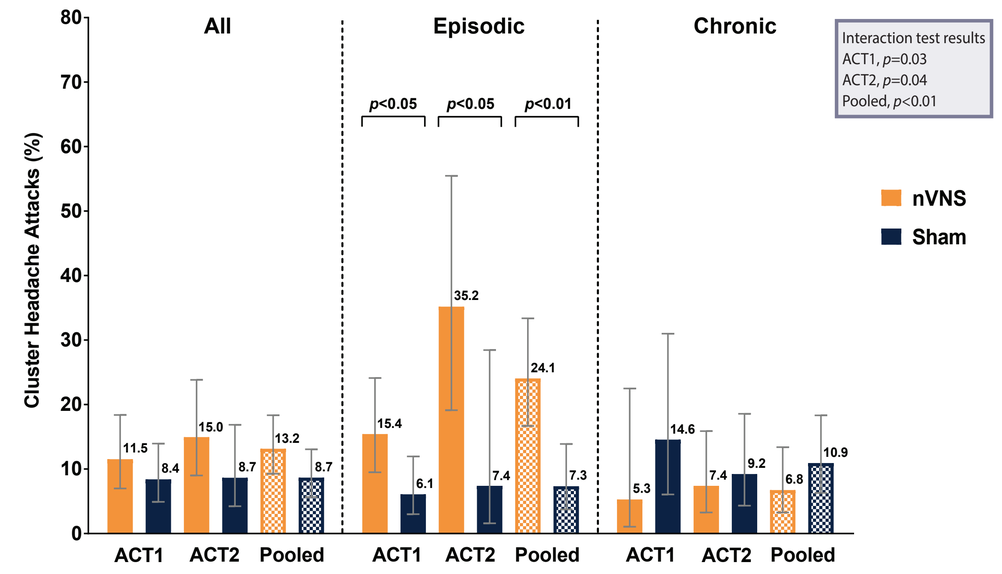
Abbreviation: SD, standard deviation.
[a] *n*=108; [b] *n*=115; [c] *n*=120; [d] *n*=103.

Figure 1. Proportion of Patients Who Achieved Responder Status at 15 Minutes (First Attack)



p Values are from logistic regression; pooled analyses included study as a covariate.
First-order interactions between treatment group and cluster headache subgroup were assessed to determine if treatment effect varied significantly by cluster headache subtype.

Figure 2. Proportion of All Treated Attacks That Achieved Pain-Free Status at 15 Minutes

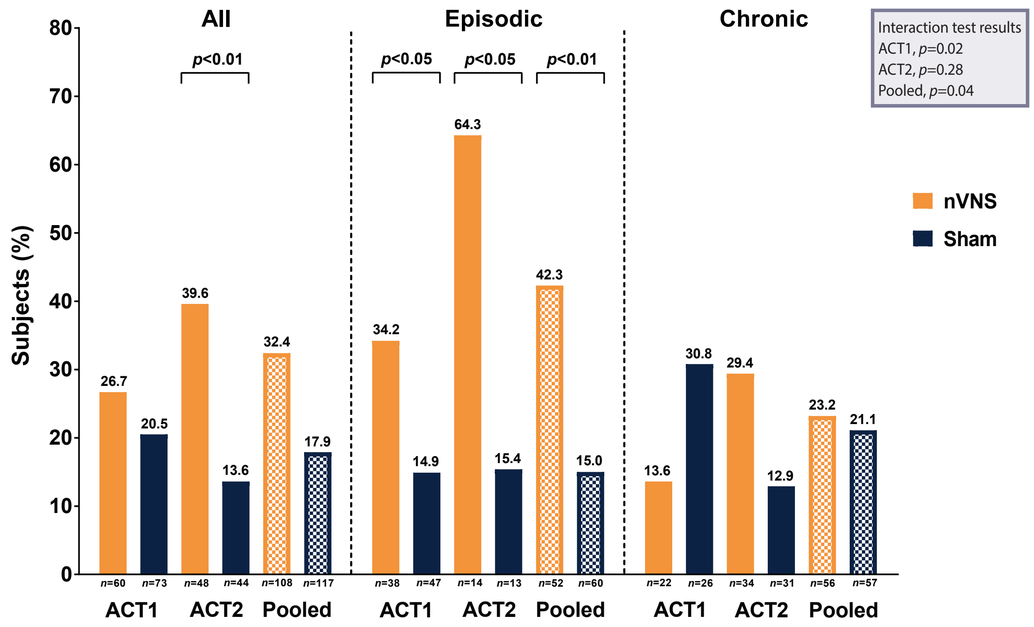


p Values are from *F* tests; pooled analyses included study as a fixed effect. Error bars denote 95% confidence intervals.
First-order interactions between treatment group and cluster headache subgroup were assessed to determine if treatment effect varied significantly by cluster headache subtype.

Conclusions

- This analysis of pooled data from 2 large trials suggests that nVNS was
  - Effective in aborting attacks in patients with episodic cluster headache, but not in those with chronic cluster headache
  - Safe and well tolerated in all patients
- nVNS has important advantages over existing treatment options for cluster headache
  - May be applied multiple times per day
  - Can be used alone or in combination with any existing acute medication for cluster headache
  - Easy-to-use, convenient, flexible
- Additional studies are warranted to explore further cluster headache disease mechanisms and possible reasons underlying the differential efficacy for nVNS between episodic and chronic cluster subtypes

Figure 3. Proportion of Patients With Responder Status at 15 Minutes for ≥50% of Attacks



p Values are from logistic regression; pooled analyses included study as a covariate.
First-order interactions between treatment group and cluster headache subgroup were assessed to determine if treatment effect varied significantly by cluster headache subtype.

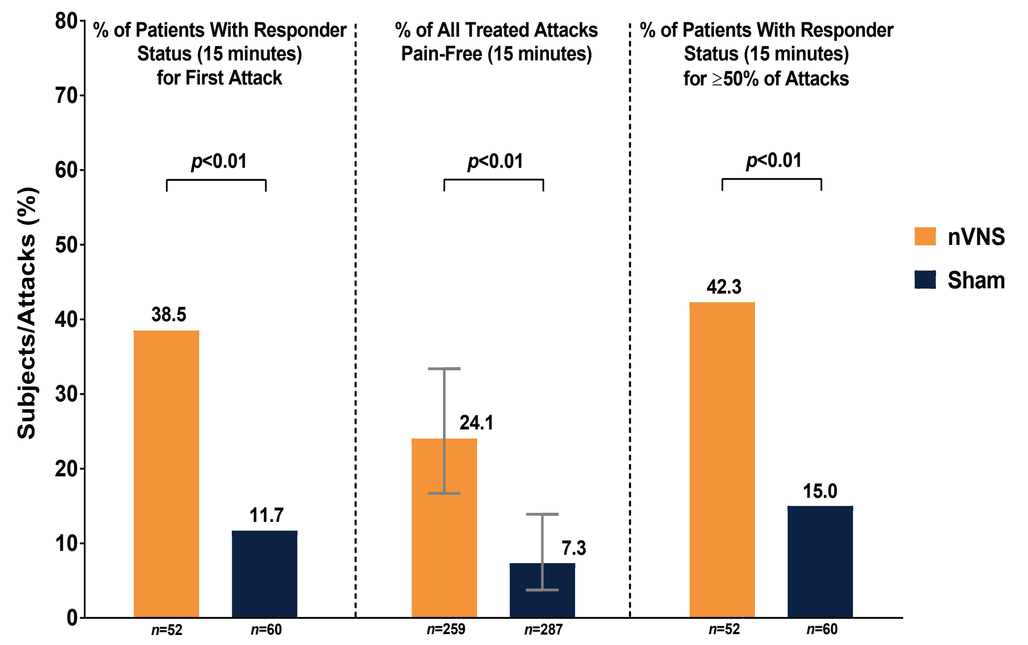
Table 3. Incidence of AEs, SAEs, and ADEs in ACT1 and ACT2 (Pooled Data)

AEs and ADEs	nVNS (*n*=123)	Sham (*n*=129)
Subject with ≥1 AE, No. (%)	38 (30.9)	45 (34.9)
Subject with ≥1 SAE, No. (%)	2 (1.6)	1 (0.8)
Subject with ≥1 ADE, No. (%)	20 (16.3)	34 (26.4)
ADEs occurring in ≥5% of subjects in either treatment group, No. (%)		
Dysgeusia	0	8 (6.2)
Erythema at treatment site	0	9 (7.0)
Perioral myokymia during treatment	8 (6.5)	0

Abbreviations: ADE, adverse device effect; AE, adverse event; SAE, serious adverse event.

- SAE reports
  - nVNS group (2 subjects)
    - Exacerbation of cluster headache
    - Lower abdominal and back pain
  - Sham group (1 subject)
    - Anxiety and depression
  - None were considered related to the study device
- No serious ADEs were reported

Figure 4. Pooled Analysis Summary (Episodic Subgroup Only)



p Values for % of patients are from logistic regression; pooled analyses included study as a covariate.
p Values for % of attacks are from *F* tests; pooled analyses included study as a fixed effect. Error bars denote 95% confidence intervals.

References

1. Silberstein SD, Mechtler LL, Kudrow DB, et al. Non-invasive vagus nerve stimulation for the acute treatment of cluster headache: findings from the randomized, double-blind, sham-controlled ACT1 study. *Headache*. 2016;56(8):1317-1332.
2. Goadsby PJ, de Coo I, Silver N, et al. Non-invasive vagus nerve stimulation for the acute treatment of episodic and chronic cluster headache: findings from the randomized, double-blind, sham-controlled ACT2 study (abstract IOR03). *Headache*. 2017;57(s3):128.

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