Received: 2 August 2023 | Accepted: 3 February 2024

DOI: 10.1002/jpn3.12174

JPGN

ORIGINAL ARTICLE

Gastroenterology

A multicenter registry study on percutaneous electrical nerve field stimulation for pediatric disorders of gut–brain interaction

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Abstract

Objectives: Percutaneous electrical nerve field stimulation (PENFS) has demonstrated promise in single-center trials for pediatric abdominal pain-related disorders of gut–brain interaction (DGBI). Our aim was to explore efficacy of PENFS as standard therapy for DGBI in a registry involving multiple pediatric gastroenterology referral centers.

Methods: This was a multicenter, prospective open-label registry of children (8–18 years) undergoing PENFS for DGBI at seven tertiary care gastroenterology clinics. DGBI subtypes were classified by Rome IV criteria. Parents and patients completed Abdominal Pain Index (API), Nausea Severity Scale (NSS), and Functional Disability Inventory (FDI) questionnaires before, during therapy and at follow-up visits up to 1 year later.

Results: A total of 292 subjects were included. Majority (74%) were female with median (interquartile range [IQR]) age 16.3 (14.0, 17.7) years. Most (68%) met criteria for functional dyspepsia and 61% had failed ≥4 pharmacologic therapies. API, NSS, and FDI scores showed significant declines within 3 weeks of therapy, persisting long-term in a subset. Baseline ($n = 288$) median (IQR) child-reported API scores decreased from 2.68 (1.84, 3.58) to 1.99 (1.13, 3.27) at 3 weeks ($p < 0.001$) and 1.81 (0.85, 3.20) at 3 months ($n = 75$; $p < 0.001$). NSS scores similarly improved from baseline, persisting at three ($n = 74$; $p < 0.001$) and 6 months later ($n = 55$; $p < 0.001$). FDI scores displayed similar reductions at 3 months ($n = 76$; $p = 0.01$) but not beyond. Parent-reported scores were consistent with child reports.

Conclusions: This large, comprehensive, multicenter registry highlights efficacy of PENFS for gastrointestinal symptoms and functionality for pediatric DGBI.

Abbreviations: DGBI, disorder of gut-brain interaction; PENFS, percutaneous electrical nerve field stimulation.

CME module may be found at https://learnonline.naspghan.org/jpgn2

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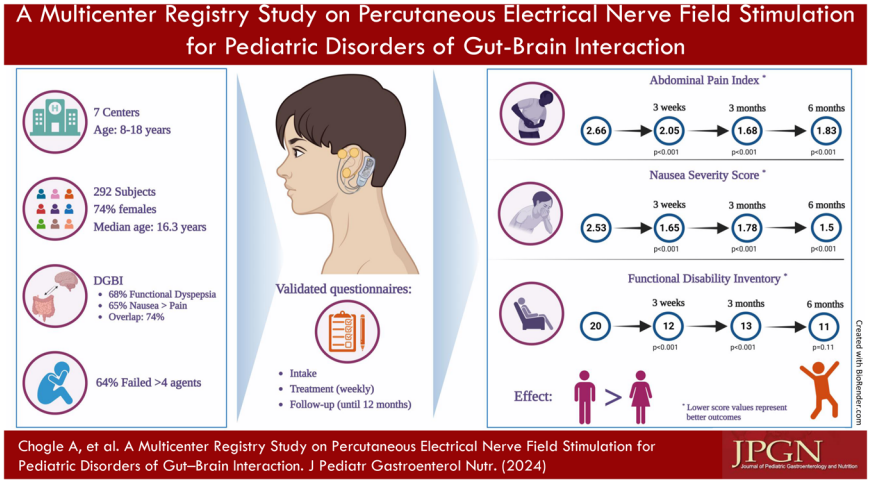
Funding information
None



KEYWORDS
functional dyspepsia, functional gastrointestinal disorders, functional nausea, neuromodulation, neurostimulation

1 | INTRODUCTION

Pediatric disorders of gut–brain interaction (DGBI) affect up to 25% of children worldwide.[1] DGBI account for 50% of all pediatric gastroenterology (GI) tertiary care referrals and are associated with functional disability, school absenteeism, and substantial healthcare costs.[2–5] Many children with DGBI continue to have symptoms into adulthood.[6] Due to lack of effective therapies, treatment is often focused on lifestyle interventions and nonpharmacologic alternatives.[7] Yet, many children are treated with neuromodulators including antidepressants. While these drugs may be effective in patients with mental health comorbidities, antidepressants are not specifically approved for DGBI and are associated with significant adverse effects. A recent Cochrane review and two systematic reviews demonstrated insufficient evidence for pharmacotherapy in children with DGBIs.[8–10]

Auricular percutaneous electrical nerve field stimulation (PENFS) is an emerging, nonpharmacological option and the only Food and Drug Administration (FDA)-cleared treatment for pediatric abdominal pain-related DGBI.[11] PENFS is applied to the external ear of choice and provides alternating frequencies (1–10 Hz) of low voltage (3.2 V) stimulation for 5 consecutive days each week.[12] The device has four percutaneously placed electrodes (three frontal and one dorsal) applied to auricular areas innervated by branches of four cranial nerves (CN V, VII, IX, and X).[13] Apart from the vagus (CN X), several of these carry parasympathetic fibers that are presumably modulated by the broader field stimulation.[14,15] PENFS acts by modulating central pain pathways, presumably via noninvasive electrical stimulation of the auricular branch of the vagus nerve.[16] Animal studies have shown decreased amygdala and spinal neuronal firing as a plausible mechanism of reduced visceral hypersensitivity.[17] Brain functional MRI studies document effects on brainstem and limbic structures after transcutaneous auricular stimulation.[18] A double-blind, randomized, controlled trial in adolescents with abdominal pain-related DGBI demonstrated improvement in pain, functional disability, and overall well-being after 3 weeks of PENFS.[12,19] An open-label PENFS study in adolescents with abdominal pain-related DGBI reported improved pain, nausea, sleep, disability, and anxiety with some effects sustained for 6-12 months.[20]

This study aimed to prospectively assess short and long-term effects on GI symptoms and functional

What is Known

- Initial single-center data demonstrate promising efficacy of percutaneous electrical nerve field stimulation (PENFS) for abdominal pain-related disorders of gut–brain interaction (DGBI).
- Presently, there are no large-scale studies on the effects of PENFS on gastrointestinal symptoms and related functional disability.

What is New

- This comprehensive, multicenter registry illustrates the beneficial effects of PENFS for pain, nausea, and functional disability in nonselected children affected by DGBI.

disability in a large, multicenter registry of consecutive, nonselected children with DGBI undergoing PENFS per standard of care.

2 | METHODS

2.1 | Study population

This was a multicenter, prospective open-label longitudinal study enrolling children ages 8–18 years who underwent PENFS per standard of care into a multicenter registry at seven pediatric outpatient GI clinics. The study was initially a single-center registry at Children's Wisconsin (CW) from September 2017 through February 2018, followed by expansion to multicenter with seven participating centers from March 2018 through May 2022. Participating sites included Children's Wisconsin (central site), Children's Hospital of Orange County, Cincinnati Children's Hospital, Atrium Health Levine Children's Hospital, Boston Children's Hospital, Riley Hospital for Children, and Texas Children's Hospital. The human research Institutional Review Board at all sites approved this study. Informed consent was provided by participating children and their legal guardian before enrollment. Data were entered electronically into the REDCap database via iPads or email distribution.

All consecutive patients ages 8–18 years diagnosed with a DGBI and referred for PENFS were invited to participate. Subjects underwent screening diagnostic tests at the discretion of the pediatric gastroenterologist. Patients were managed per standard practice conditions and no research interventions other than symptom surveys were performed. Data were collected for up to 12 weeks of consecutive PENFS therapy. Registry exclusion criteria were significant developmental delays, active organic gastrointestinal conditions as suspected sole cause of symptoms, enteral tube feedings, total parenteral nutrition or lack of English proficiency. Other pharmacologic therapy and treatment interventions were continued per standard of care.

2.2 | Study design

Data collection included demographics, diagnostic testing, prior failed medications as well as specific comorbidities and medical history. Comorbidities/diagnoses collected included: migraine headache, autonomic dysfunction, psychiatric disorder, joint hypermobility, fibromyalgia, and sleep disturbance. Subjects were grouped by number of previously failed prescription medications (0–3, 4–6, 7–9, and ≥10). Patients and their legal guardians completed the surveys at baseline and weekly during therapy. A subset of patients completed follow-up surveys every 3 months up to 1-year post therapy.

1. Rome IV Diagnostic Questionnaire on Pediatric Functional Gastrointestinal Disorders[21]: self-report survey assessing GI symptoms for clinical classification into Rome IV criteria. Administered at baseline.
2. Abdominal Pain Index (API; child and parent report)[22]: instrument assessing abdominal pain characteristics (frequency, severity, duration) modified to collect data over the past week rather than past 2 weeks. Administered at baseline, weekly during therapy, and at any follow-up visits.
3. Nausea Severity Scale (NSS; child and parent report)[23]: instrument assessing nausea characteristics (frequency, severity, duration) modified to collect data over the past week. Administered at baseline, weekly during therapy, and at any follow-up visits.
4. Functional Disability Inventory (FDI; child and parent)[24]: measure of physical and psychosocial functioning. Administered at baseline, weekly during therapy, and follow-up visits.

Trained and certified medical professionals placed the PENFS devices weekly on subjects, who wore the device for 5 days (day and night) followed by removal by family. The stimulation may or may not be perceived by the patient. The device was placed on the subject's preferred side (usually guided by sleeping position) but switched as needed per subject preference or local skin irritation. Most subjects received 4 consecutive weeks of therapy. The primary endpoint was abdominal pain severity (API) after 3 weeks, when patients presented for placement of the 4th device, as most did not return the subsequent week. Outcomes were assessed at baseline and weekly until last visit (generally after Week 3, at the 4th device placement) as well as during follow-up time points when possible.

2.3 | Statistical analysis

Continuous variables were summarized as median (25^{thle}, 75^{thle}: interquartile range [IQR]) and groups compared using a Mann–Whitney test, a Wilcoxon paired test within groups. The *p*-values were approximate when there were several ties. Categorical variables were summarized as *n* (%), using a Fisher exact test to compare groups and a McNemar exact test within groups. A result was reported as statistically significant for an unadjusted, two-sided $p < 0.05$. Data analyses were performed using SAS 9.4 and SPSS 28.0 software.

3 | RESULTS

3.1 | Demographics and medical history

A total of 371 patients were enrolled and 292 had sufficient data on at least one of the three outcome surveys for inclusion in analyses; the number of subjects per participating center and racial distribution are listed in Table 1. Thirty-eight (13%) subjects withdrew from therapy within the first 3 weeks for the following reasons: symptom improvement/treatment success ($n = 12$), lack of response/continued medical problems ($n = 8$), non-compliance ($n = 8$), side effects ($n = 6$), and unknown ($n = 4$). Males who withdrew had a higher BMI compared to those who were retained ($p = 0.02$). There were no other significant differences in demographics, comorbidity burden or baseline symptom scores between subjects who withdrew and those retained. The majority were female ($n = 216$; 74%). The median (IQR) age was 16.3 (14.0, 17.7) years. Females and males were similar in age: median (IQR) 16.3 (14.2, 17.7) versus 16.0 (13.3, 17.3) years respectively ($p = 0.22$). There were no gender differences by race. Table 2 shows the distribution of Rome IV diagnoses and comorbidities by gender. The majority (67.8%) met Rome criteria for functional dyspepsia postprandial distress syndrome and 74.3% had overlapping Rome criteria (met more than one diagnostic criteria). Irritable bowel syndrome was significantly more common in males. Of the entire cohort, 65.8% endorsed nausea as more bothersome than abdominal pain. Autonomic dysfunction and fibromyalgia were significantly more common in females.

TABLE 1 Participating centers and racial distribution.

Participating centers	
Center	**Number of patients**
Cincinnati Children's Hospital	89
Children's Hospital of Orange County	75
Children's Wisconsin	65
Atrium Health Levine Children's Hospital	31
Boston Children's Hospital	18
Riley Hospital for Children	11
Texas Children's Hospital	3
Racial Distribution	
Race	**Percentage**
Caucasian	92.8
Hispanic	4
African American	1.8
Asian	1.1
Mixed Race	0.4

3.2 | Abdominal pain

Child median (IQR) API scores of the entire cohort improved significantly from baseline ($n = 288$) 2.68 (1.84, 3.58) to 1.99 (1.13, 3.27) at 3 weeks ($n = 209$; $p < 0.001$). Further reductions were observed at 3 months ($p < 0.001$) and 6 months ($p < 0.001$; Figure 1) but with a declining number of participants ($n = 75$ and $n = 60$ respectively; Table 3). For the remaining subjects, effects were sustained at 9 ($p = 0.002$) and 12-month ($p < 0.001$) follow-up visits. Table 3 displays API scores for the entire cohort and by gender. Parent-reported API scores were consistent with child reports.

3.3 | Nausea

Child median (IQR) NSS scores similarly improved from baseline ($n = 282$) 2.53 (1.50, 3.50) to 1.65 (0.35, 2.80) at 3 weeks ($n = 200$; $p < 0.001$) and stayed significantly reduced at 3 ($n = 74$; $p < 0.001$) and 6 months ($n = 55$; $p < 0.001$). Table 3 shows NSS scores for the entire cohort and by gender. Parent-reported scores were overall consistent with child reports.

3.4 | Functional disability

Child median (IQR) FDI scores decreased across time from baseline ($n = 290$) 20 (9.0, 29.0) to 12.0 (4.0, 24.0) at 3 weeks ($n = 209$; $p < 0.001$). Scores stayed persistently low at 3 months ($n = 76$; $p = 0.01$) but not at subsequent follow-up. See Table 3 for complete data and distribution of FDI scores by gender. There was significant improvement in disability by Week 3. The proportion of subjects with moderate or severe disability declined from 48.3% at baseline to 33.6% at Week 3 ($p < 0.001$). Parent-reported scores were overall consistent with child reports with significant score reductions from baseline until 3 months follow-up.

Subanalyses of the most prevalent DGBI diagnoses (functional dyspepsia postprandial distress syndrome, functional constipation, irritable bowel syndrome, and functional nausea) demonstrated no statistical differences in pain, nausea, or disability outcomes at 3 weeks and 3 months follow-up whether or not patients met these Rome criteria.

3.5 | Medication burden and side effects

A total of 92.1% of 280 subjects had failed prior prescription drug therapy for DGBI symptoms; 61.4% failed ≥4, 30.0% failed ≥7%, and 13.2% failed ≥10 different drugs. The proportion of previously failed drugs/drug classes were as follows: antiemetics (62%),

TABLE 2 Comparisons of Rome diagnosis and comorbidities by gender.

	All ($n = 292$) n (%)	Females ($n = 216$) n (%)	Males ($n = 76$) n (%)	p
Rome IV diagnosis				
Functional Dyspepsia Post Prandial Distress Syndrome	198 (67.8)	153 (70.8)	45 (59.2)	0.065
Functional constipation	187 (64.0)	135 (62.5)	52 (68.4)	0.41
Irritable Bowel Syndrome	56 (19.2)	33 (15.3)	23 (30.3)	**0.006**
Functional nausea	50 (17.1)	36 (16.7)	14 (18.4)	0.73
Functional vomiting	47 (16.1)	35 (16.2)	12 (15.8)	>0.99
Functional Dyspepsia Epigastric Pain Syndrome	40 (13.7)	34 (15.7)	6 (7.9)	0.087
Rumination	22 (7.5)	17 (7.9)	5 (6.6)	0.81
Abdominal migraine	16 (5.5)	13 (6.0)	3 (3.9)	0.77
Aerophagia	16 (5.5)	13 (6.0)	3 (3.9)	0.77
Cyclic Vomiting Syndrome	8 (2.7)	6 (2.8)	2 (2.6)	>0.99
Functional Abdominal Pain NOS	4 ((1.4)	3 (1.4)	1 (1.3)	>0.99
Nonretentive fecal incontinence	0 (0)	0 (0)	0 (0)	NA
Overlapping Rome criteria	217 (74.3)	160 (74.0)	57 (75.0)	0.79
≥3 different Rome criteria	116 (39.7)	87 (40.3)	29 (38.2)	0.83
Comorbidities				
Migraine headache	105 (36.0)	79 (36.6)	26 (34.2)	0.78
Autonomic dysfunction	101 (34.6)	83 (38.4)	18 (23.7)	**0.03**
Psychiatric disorder	85 (29.1)	66 (30.6)	19 (25.0)	0.38
Joint hypermobility	82 (28.1)	67 (31.0)	15 (19.7)	0.08
Sleep disturbance	36 (12.3)	28 (13)	8 (10.5)	0.69
Fibromyalgia	18 (6.2)	17 (7.9)	1 (1.3)	**0.05**

Note: Bold values indicate statistically significant at $p < 0.05$. Percentages reflect fraction of total and within each gender based on sample size $n = 292$.
Abbreviation: NOS, not otherwise specified.

cyproheptadine (40%), tricyclic antidepressants (37%), prescription pain medications including antispasmodics (25%), neuropathy medications (24%), laxatives (23%), selective serotonin reuptake inhibitors (20%), acid suppressants (15%), antianxiety medications (8%), and beta-blockers (4%). There were no gender differences in number of previously failed drugs ($p = 0.18$). After 3 weeks of therapy, females who had failed 0–3 prior prescription drugs had significantly lower NSS scores compared to those who had failed ≥10 drugs based on both child and parent report (both $p < 0.03$). There were no such differences in API or FDI scores between the different categories of number of drugs failed.

Adverse reactions were assessed at Week 3 after the final device application or sooner in cases of dropout. A total of 95 subjects (33%) reported 120 events of adverse reactions. The following events were reported: ear discomfort (53), allergic dermatitis (41), headache (17), nausea/vomiting (5), and dizziness (3). There was one

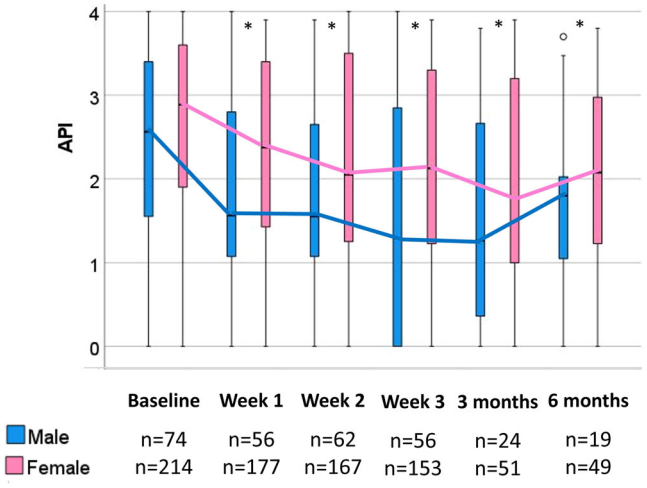


FIGURE 1 Abdominal Pain Index (API) scores over time and by gender, showing reduction in abdominal pain scores from baseline at all time points ($p < 0.05$).

TABLE 3 Median (interquartile range [IQR]) scores by gender for Abdominal Pain Index (API), Nausea Severity Scale (NSS), and Functional Disability Inventory (FDI) over 12 months follow-up.

Abdominal Pain Index (API)				API female			API male		
Time point	***n***	**Median (IQR)**	***p* Value**	***n***	**Median (IQR)**	***p* Value**	***n***	**Median (IQR)**	***p* Value**
Baseline	288	2.68 (1.84, 3.58)	N/A	214	2.90 (1.91, 3.6)	N/A	74	2.56 (1.58, 3.40)	N/A
3 weeks	209	1.99 (1.13, 3.27)	**<0.001**	153	2.13 (1.2, 3.3)	**<0.001**	56	1.59 (0, 3.01)	**<0.001**
3 months	75	1.81 (0.85, 3.20)	**<0.001**	51	2.0 (1.0, 3.2)	**<0.001**	24	1.55 (0.54, 2.96)	**<0.001**
6 months	60	1.70 (0.93, 2.72)	**<0.001**	49	1.88 (1.23, 2.88)	**0.016**	19	1.83 (0.70, 2.05)	**0.003**
9 months	26	1.90 (1.33, 2.82)	**0.002**	18	1.88 (1.31, 2.64)	0.061	8	2.15 (1.35, 3.10)	**0.025**
12 months	22	2.20 (0.41, 3.21)	**<0.001**	12	2.55 (0.69, 3.38)	**0.028**	10	1.39 (0, 2.47)	**0.008**
Nausea Severity Scale (NSS)				**NSS female**			**NSS male**		
Time point	***n***	**Median (IQR)**	***p* Value**	***n***	**Median (IQR)**	***p* Value**	***n***	**Median (IQR)**	***p* Value**
Baseline	282	2.50 (1.50, 3.50)	N/A	208	2.50 (1.55, 3.55)	N/A	74	2.48 (1.19, 3.2)	N/A
3 weeks	200	1.73 (0.35, 2.80)	**<0.001**	146	1.90 (0.83, 2.90)	**<0.001**	54	1.25 (0, 2.25)	**<0.001**
3 months	74	1.75 (0.44, 2.88)	**<0.001**	51	1.85 (1.0, 2.88)	**<0.001**	23	1.50 (0, 2.45)	0.077
6 months	55	1.50 (0.64, 2.50)	**<0.001**	39	1.50 (0.95, 2.8)	**0.009**	16	1.50 (0.95, 2.50)	0.056
9 months	25	2.13 (1.40, 2.95)	0.149	17	2.15 (1.33, 3.0)	0.109	8	1.90 (1.4, 3.35)	0.753
12 months	15	1.80 (0, 3.15)	0.005	9	3.0 (0.7, 3.8)	0.107	6	0.90 (0, 1.95)	0.068
Functional Disability Inventory (FDI)				**FDI female**			**FDI male**		
Time point	***n***	**Median (IQR)**	***p* Value**	***n***	**Median (IQR)**	***p* Value**	***n***	**Median (IQR)**	***p* Value**
Baseline	290	19.0 (9.0, 29.0)	N/A	214	20.0 (10.0, 29.0)	N/A	76	17.0 (7.0, 27.8)	N/A
3 weeks	209	12.4 (4.0, 24.0)	**<0.001**	154	14.0 (4.0, 24.0)	**<0.001**	55	9.5 (1.0, 24.3)	**<0.001**
3 months	76	12.9 (4.0, 22.8)	**0.010**	52	13.0 (5.0, 23.5)	**0.041**	24	10.0 (0, 22.3)	0.190
6 months	59	9.8 (1.8, 26.3)	0.109	40	19.0 (3.2, 28.0)	0.295	19	6.0 (0, 26.0)	0.202
9 months	26	10.0 (4.8, 28.0)	0.532	18	15.0 (5.0, 32.5)	0.906	8	7.0 (5.0, 19.0)	0.674
12 months	21	9.0 (1.5, 29.4)	0.417	11	27.9 (1.5, 32.1)	0.332	10	6.0 (0, 9.0)	**0.092**

Note: Bold values indicate statistically significant at $p < 0.05$.

case of unilateral, reduced hearing which resolved upon cessation of therapy. Of the reported adverse events, 80% were classified as mild (i.e., local discomfort or minor skin irritation that resolved upon device removal) and 20% as moderate (i.e., more significant discomfort or skin irritation/rash requiring lead adjustment and/or alternating side of device placement). There were no serious adverse events.

The PENFS device was initially placed on right versus left ear in similar number of cases (56% vs. 44%; $p = \text{NS}$) and remained statistically similar for subsequent placements and only alternated in cases of skin irritation, discomfort with sleeping, and so forth.

4 | DISCUSSION

This prospective, uncontrolled, large-scale multicenter study on PENFS therapy expands the existing literature in children with DGBI.[12,19,20] A randomized, double-blind trial demonstrated superiority of PENFS over placebo using pain, global well-being, and functional disability endpoints.[12] However, other reports have been relatively small.[20,25] The impetus for the current registry study was a need to examine PENFS effects in a larger cohort across multiple sites and particularly, the effects on consecutive patients in a real-world setting, without strict inclusion/exclusion criteria. As defined by the FDA, real-world data signifies the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of real-world evidence.[26] This study was an opt-in, prospective registry capturing all consecutive DGBI patients treated per standard of care across seven tertiary care pediatric gastroenterology centers. The registry thus likely included children with a greater symptom and comorbidity burden than expected in the general pediatric population. This is evidenced by the large number who had already failed pharmacological therapy (92%) and the large proportion (74%) of

children with DGBI overlap and significant comorbidities. Consecutive patients were enrolled and not selected to participate based on specific inclusion criteria other than meeting Rome criteria for a DGBI. There was no correlation between specific Rome criteria and symptom response, indicating that DGBI diagnoses are not specific or mutually exclusive nor predictive of treatment response. The lack of monetary incentives may have affected the willingness to participate in later follow-up visits, as evidenced by decreased participation over time.

Although an uncontrolled study, the therapeutic effectiveness of PENFS in a large cohort of tertiary care DGBI patients is underscored by our data. Significant alleviation in abdominal pain and nausea was noted at 3 weeks and 3 months in a larger subset (>70 subjects), followed by longer term for a smaller subset. Unfortunately, the significant number of patients lost to extended follow-up makes it difficult to understand the long-term sustainability of PENFS. The increase in API and NSS scores among females at the 6- and 12-month mark likely indicates that repeat PENFS courses are necessary, supported by recent data on median response duration of 113 days in pediatric cyclic vomiting syndrome.[27] On the contrary, a prior PENFS study noted sustained benefits up to 12 months post treatment.[20] To our knowledge, there are no comparable long-term data with other auricular neurostimulation modalities or auricular acupuncture. The premise of PENFS is to provide field stimulation across the auricle with percutaneously placed electrodes that overcome the skin resistance problems faced with transcutaneous modalities.[28] The ear locations targeted with acupuncture are in specific "acupoints" whereas the PENFS electrodes are placed alongside neurovascular bundles to create a "field" effect. While there may be similarities to acupuncture, the FDA has cleared the PENFS as a neuromodulation device.[11] Moreover, while acupuncture sessions are brief and intermittent, the PEFNS device is worn for most of the week across several consecutive weeks. Furthermore, the changing polarity across all electrodes every cycle (few seconds) allows for continuous stimulation without nerve attenuation. This likely provides a more durable response as indicated by this study and prior trials.

Our findings also spotlight an important trend in the improvement of functional capability in pediatric DGBI patients during the early weeks and months of PENFS. Over time, the FDI scores appear to stabilize, or even inch upwards, particularly in females, with no significant change detected at 12 months. This underscores the necessity of continuous monitoring and the potential need for supplemental therapies or repeat PENFS cycles.

Our research has highlighted gender-based differences in treatment outcomes that require further investigation. It is essential to extend our observations beyond 1 year and assess patient features associated with treatment response, to gain insights into the long-term sustainability of a 4-week PENFS. Exploring this new area could lead to a deeper understanding of DGBI and ultimately enhance our treatment methods in this field.[20]

Sustained clinical improvements after a relatively short period of therapy is similarly demonstrated with psychological interventions such as biofeedback, cognitive behavioral therapy, and/or guided imagery.[29–32] One study reported long-term benefits of 4–8 weeks of gut-directed hypnotherapy in pediatric DGBI with male sex as predictor of treatment success.[33] This is similar to the current study where males demonstrated greater improvement in functional disability although males had lower baseline disability scores. Other than more females suffering from dysautonomia and fibromyalgia, there were no gender differences such in demographics, prior medication burden, number of Rome diagnoses, or comorbidities to explain these baseline differences. One study demonstrated that gut-directed hypnotherapy results in reduced functional brain connectivity between inferior parietal lobe and the insula, a region associated with abnormal pain processing in DGBI.[34–37] Interestingly, increased insular connectivity correlating with reduced pain scores was found after PENFS in adults with fibromyalgia.[38] Although speculative, it is conceivable that altered brain connectivity may be responsible for the long-term improvements. Other proposed PENFS mechanisms to some degree supported by data include: (1) restoration of inefficient cardiac vagal regulation or autonomic control, (2) alterations in intestinal microbial pathways, and (3) neuromodulation of the limbic system, previously demonstrated in a preclinical study.[16,17,39,40] Multiple, conjoined mechanisms may also be at play and more studies of pathophysiology and long-term effects of PENFS are needed. These data are suggestive that PENFS at least in part targets the gut-brain axis dysregulation of DGBI.

PENFS treatment success should be viewed in relation to the suboptimal success and poor side effect profile of commonly used off-label medications. One property shared by the most commonly used drugs is anticholinergic effects. The long-term effects of blocking acetylcholine release in specific brain regions, particularly in the developing brain, are unknown. This mechanism is entirely different from PENFS and responsible for the less desirable side effects of anticholinergic drugs, which have inhibitory effects on cardiac vagal signaling.[41] Some of these medications include TCAs, SSRIs, cyproheptadine, and antispasmodics. Interestingly, many subjects in the study had failed these medications and it is unclear how this impacts outcomes in a potentially "skewed" population. In other words, it is not known if these "sicker" patients presenting to tertiary care centers are more likely to

respond to PENFS or would the outcomes be better in uncomplicated DGBI patients with fewer comorbidities and shorter symptom duration. Similar to other studies, we found significant improvements in not just abdominal pain, but also nausea and functional disability, which are relatively important in terms of patient outcomes and quality of life.[42,43] The favorable side effect profile of PENFS compared to pharmacotherapy makes it a viable alternative. While side effects such as site pain or adhesive reactions were very commonly reported (33% of subjects), they were graded as mild and there were no serious adverse events. Furthermore, only 16% of the subjects dropped out because of side effects during the treatment intervention. As local ear discomfort and adhesive reactions can be addressed by simple electrode adjustments or alternating the side of placement, these mild side effects typically do not result in subject dropout.

While this is a large, multicenter study, it has important limitations. It is well known that patients with DGBI have a high placebo response, a limitation that cannot be ignored. On the other hand, the majority of patients had already failed other interventions making a placebo effect less likely, as they were generally followed by the same team. Additional studies indicating that PENFS effects are unlikely solely via placebo include a randomized trial demonstrating superiority over sham, animal data showing reduced central neuronal firing, altered mechanosensitivity after PENFS in children with DGBI, and sustained brain connectivity changes after PENFS.[12,17,20,38] Also, as previously noted, this is a complex tertiary care population that may not be generalizable to all DGBI in the general population. Many patients did not complete the follow-up surveys, and it is possible that those that who completed them were more satisfied with treatment and willing to complete questionnaires without being incentivized. Several subjects also dropped out of therapy during the first few weeks, accounting for missing data. It is unknown if some of these, documented as "noncompliance" or "unknown" cause, may have been due to the cosmetic appearance of the device. However, our records indicate that more dropouts occurred due to treatment success than failure. Further analyses of the subjects lost to follow-up compared to those retained showed no major differences in demographics, comorbidities or baseline survey results. While the reliability of the long-term follow-up data beyond 6 months can be questioned, the results of the primary outcome and 3-month follow-ups included a fairly large cohort and is highly consistent with prior studies. These data replicate a prior randomized trial in pediatric DGBI, showing significant treatment effects compared to sham for 2–3 months and more recent, open-label data.[12,25,27,44] The results may also be skewed, perhaps underestimated, since data was not systematically collected after the end of therapy at 4 weeks due to majority not returning to clinic after the 4th device placement. Another important limitation is that we did not control for any other interventions such as medication changes or dosing adjustment that could have been given during PENFS. Finally, this is a very heterogenous population with several types of DGBI classified based on the current Rome criteria. Predicting outcomes by "symptom-based criteria" is difficult as demonstrated by our data showing no differences in outcomes when analyzed by the most common Rome categories. It is important to continue to explore the pathophysiology of these disorders to better predict outcomes to available therapies.

In conclusion, this large, multicenter open label prospective study documents efficacy of PENFS in the real-world setting. Notably, the majority of patients in these tertiary care settings had already failed previous pharmacotherapy. Although limited by a large number of dropouts, results are suggestive of a durable response in at least a subset of patients. Further exploration of specific characteristics of treatment responders and duration of optimal therapeutic effects are warranted.

ACKNOWLEDGMENTS

The authors wish to thank Elisa Ornelas (Children's Hospital of Orange County), Catherine Opladen (Atrium Health Levine Children's Hospital), Louis Pawela (Medical College of Wisconsin), Mary Berwanger (Cincinnati Children's Hospital Medical Center), Emily Ragozzino (Indiana University), Anna Akkara and Elizabeth Burch (Children's Hospital Boston), Alisara Damrongmanee (Chiang Mai University, Thailand) and Anundorn Wongteerasut (Phramongkutklao College of Medicine, Thailand) for their work on data collection, organization and entry.

CONFLICTS OF INTEREST STATEMENT

Katja Karrento: Advisory board for Abbvie and consultant for Takeda Pharmaceuticals and Neurogastrx. Samuel Nurko: Advisory board for Abbvie and Neuraxis. Rachel Rosen: Advisory board for Neuraxis. Khalil El-Chammas: Advisory board for Neuraxis. The rest of the authors report no conflicts of interest.

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How to cite this article: Chogle A, El-Chammas K, Santucci N, et al. A multicenter registry study on percutaneous electrical nerve field stimulation for pediatric disorders of gut–brain interaction. *J Pediatr Gastroenterol Nutr*. 2024;78:817-826. doi:10.1002/jpn3.12174