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Effect of percutaneous electrical nerve field stimulation on mechanosensitivity, sleep, and psychological comorbidities in adolescents with functional abdominal pain disorders

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Abstract

Background: Percutaneous electrical nerve field stimulation (PENFS) improves symptoms in adolescents with functional abdominal pain disorders (FAPDs). However, little is known about its impact on sleep and psychological functioning. We evaluated the effects of PENFS on resting and evoked pain and nausea, sleep and psychological functioning, and long-term outcomes.

Methods: Patient ages 11–19 years with FAPD requiring PENFS as standard care were recruited. Evoked pain was elicited by a Water Load Symptom Provocation Task (WL-SPT) before and after four weeks of treatment. Pain, gastrointestinal symptoms, sleep, somatic symptoms, and physical and psychological functioning were assessed. Actigraphy was used to measure daily sleep-wake patterns.

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AUTHOR CONTRIBUTIONS

Dr. Neha R Santucci designed and conducted the study and wrote the manuscript. Drs. Robert Coghill and Christopher King mentored Dr. Santucci, conceived the idea for the study, and edited each iteration through the final draft. Dr. Coghill provided the Visual Analog Scales. Dr. King provided the Actigraphy watches and read the Actigraphs for the study. Drs. El-Chammas and Graham recruited patients from their clinics, provided expertise in PENFS and FAPD, and edited each iteration of the manuscript. Drs. Rashmi Sahay and Lin Fei organized the data and performed data analyses for the study. Cheryl Jones RN, Drs. Alisara Damrongmanee, and Anundorn Wongteerasut helped in recruiting patients and data collection. Cheryl Jones assisted in long-term follow-up. Dr. Natoshia Cunningham provided guidance and expertise in FAPD, and research methodology (e.g., conducting water load symptom provocation task), reviewed and helped interpret the water load data, and provided substantive feedback and edits to each iteration through the final draft.

COMPETING INTEREST

The authors have no competing interests.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

Key Results: Twenty patients (14.3 ± 2.2 years old) with FAPD were enrolled. Most patients were females (70%) and white (95%). During pain evoked by WL-SPT, visual analog scale (VAS) pain intensity and nausea were lower following PENFS compared with baseline ($p = 0.004$ and $p = 0.02$, respectively). After PENFS, resting VAS pain unpleasantness ($p = 0.03$), abdominal pain ($p < 0.0001$), pain catastrophizing ($p = 0.0004$), somatic complaints (0.01), functional disability ($p = 0.04$), and anxiety ($p = 0.02$) exhibited significant improvements, and some were sustained long-term. Self-reported sleep improved after PENFS ($p's < 0.05$) as well as actigraphy-derived sleep onset latency ($p = 0.03$).

Conclusions and Inferences: We demonstrated improvements in resting and evoked pain and nausea, sleep, disability, pain catastrophizing, somatic complaints, and anxiety after four weeks of PENFS therapy. Some effects were sustained at 6–12 months post-treatment. This suggests that PENFS is a suitable alternative to pharmacologic therapy.

Keywords

functional abdominal pain; irritable bowel syndrome; nerve stimulation; pediatrics; sleep

1 | INTRODUCTION

Functional abdominal pain disorders (FAPDs) are among the most common pediatric pain disorders.[1] Pain-associated impairment is prevalent in approximately one third of those affected,[2–4] and poor treatment outcomes are associated with significant psychosocial dysfunction.[5,6] The manifestations of chronic abdominal pain are associated with underlying visceral hyperalgesia,[7,8] disturbances in sleep,[9–12] and/or psychological comorbidities,[13–18] but the cause-and-effect relationship is unknown. Visceral hyperalgesia is an altered sensation in response to non-noxious, physiological stimuli in the gastrointestinal (GI) tract and is often impacted by psychosocial factors.[7,8,13] Adolescents with FAPD have a higher incidence of depression or anxiety (40–50%).[2,14] Catastrophizing and somatization have shown to result in worse psychosocial and functional outcomes.[15–18] Sleep disturbances may be a result of pain, but have also been suggested to worsen pain in children with chronic pain conditions.[19–24] Preclinical and clinical data have shown increased pain sensitivity with sleep deprivation, and there is some suggestion that interventions directed toward sleep improve pain.[25–28] All of these factors potentially contribute to the severity of symptoms in FAPD. Pain has different cognitive and affective elements and can be assessed as resting or induced (evoked) pain.[29] To better understand the FAPD pain experience, induced visceral pain[30] can provide a better insight into a patient's symptoms compared with retrospective reports and questionnaires that assess resting pain.

Percutaneous electrical nerve field stimulation (PENFS) is a noninvasive emerging treatment for adolescents with functional abdominal pain associated with irritable bowel syndrome (IBS). A randomized controlled trial of PENFS in adolescents with FAPD showed significant improvement in worst pain scores, global well-being, and functional disability compared with sham.[31] It has shown to decrease firing of neurons in the amygdala in animal models.[32] To date, little is known about the impact on factors that influence symptoms, or the long-term duration of benefits post-treatment. The vagal parasympathetic tone before falling asleep regulates the sleeping drive,[33] and impaired vagal nerve efficiency has

shown to predict a response to PENFS.[34] While the interaction between sleep, visceral hyperalgesia, evoked pain, and psychological comorbidities remains poorly understood, determining how PENFS influences these contributory factors may help better understand the benefits to patients and uncover the underlying mechanism.

The primary aim of this study was to evaluate the effects of PENFS on resting and evoked abdominal pain and nausea before and after symptom provocation [via a waterloading test]. We also examined if sleep would improve during, and psychological functioning would improve during and following PENFS. Lastly, we explored the predictors of treatment response, effects of medications and symptom duration, and factors mediating the relationship between sleep and abdominal pain. We hypothesized that PENFS would improve both resting and evoked pain, nausea, and sleep as well as positively impact psychological well-being and disability, both short- and long-term.

2 | METHODS

After obtaining institutional review board approval, adolescents aged 11–19 years with who met the Rome IV criteria for nonepisodic functional abdominal pain disorders [(functional dyspepsia (FD), IBS, and functional abdominal pain-not otherwise specified (FAP-NOS)] and who agreed to receive PENFS as part of their routine clinical care were recruited. Exclusion criteria included pregnancy, diabetes, adhesive allergy, implanted electrical devices, GI inflammatory disorders, feeding disorders/tube feedings, major heart diseases, eating or conversion disorders, and disorders of cognitive impairment.

2.1 | Study timeline

All subjects had five weekly clinic visits, four included device placement each week, while the fifth was a follow-up 2–3 days following treatment. Patients were treated with PENFS for four weeks following a standard treatment protocol.[31] No new medications were started, and patients remained on a stable medication dose two weeks prior to and during treatment.

After obtaining written informed consent, information on demographics, Rome IV Diagnostic Questionnaire on Pediatric Functional Gastrointestinal disorders,[35] past medical history including any self-reported sleep disorder, and medications affecting sleep were collected at the initial visit. Patients completed baseline sleep and psychological questionnaires before device placement. Patients performed the Water Load Symptom Provocation Task (WL-SPT)[30] as outlined below twice: before initial device placement at the first visit and after completion of treatment at the follow-up visit. Patients received an Actiwatch[36,37] to measure daily sleep-wake patterns for the duration of the treatment. Follow-up sleep questionnaires and psychological measures were obtained at different time points during the clinic visits. Patients were contacted by phone, and additional questionnaires were completed 6–12 months after the last treatment to assess long-term benefit (Table 1).

2.1.1 | 2.2 PENFS treatment—IB-stim® (Innovative Health Solutions, Versailles, IN, USA) is an external auricular device with a battery powered generator that creates PENFS, targeting cranial nerves V, VII, IX, and X.[31] It delivers a current of 3.2 volts with a

rectangular pulse wave and has alternating frequencies of 1 ms pulses of 1 and 10 Hz every 2 seconds. It delivers stimulation in cycles of 2 hours on and 35 min off. After obtaining consent, the certified and trained physician placed the device each week for four weeks. The device was placed in the appropriate position on the desired ear and secured with sterile dressings. Patients removed the device after five days and returned the following week for device replacement. Thus, each week consisted of five days with the device on and two days off.[31]

2.1.2 | 2.3 Study tasks

2. 3. 1. Water load symptom provocation task (WL-SPT): The WL-SPT is a safe and noninvasive validated technique to induce visceral pain in children ages 8–16 years with FAPD.[8,30,38] Participants were given 1.5 L of water to drink at their own pace over 15 min or until they felt “completely full” on the Fullness Rating Scale.[8] Patients completed the VAS pain intensity, unpleasantness, and nausea scales before, immediately after, 5 and 10 min after WL-SPT.

2.2 | 2.3.2 Actigraphy

An Actiwatch (Respironics, Bend, OR; http://www.actigraphy.respironics.com) was used to measure daily sleep-wake patterns and record body movements (sensitivity of >0.01 g force) after first device placement for a total of four weeks.[36] This device has good reliability and validity in individuals with chronic pain.[37] Baseline actigraphy data prior to PENFS were not obtained due to the nature of the study. The measures generated included time in bed, total sleep time, sleep efficiency (percentage of the estimated total sleep time and time spent in bed), sleep latency (duration in minutes to fall sleep), wake after sleep onset (WASO–time spent awake after going to sleep), and sleep onset variability (each patient’s personal standard deviation in sleep onset).[22–24]

2.3.3 Sleep diaries—To corroborate sleep and activity, participants were instructed to complete a daily diary in the evening and morning during the study. It captured information about daily sleep quality and numeric ratings of pain on a Likert scale from 1 to 10.

2.2.1 | 2. 4 Measures

2.4.1 Measures completed during WL-SPT

Pain intensity/unpleasantness visual analog scale (VAS)[29,39].: Visual analog scale consists of a plastic slide rule with a 15-cm excursion anchored with the words “no pain” versus “most intense pain imaginable” for pain intensity and “no pain unpleasantness” versus “most pain unpleasantness” for unpleasantness, respectively. Numbers on the back of the scale ranged from 0 to 10.[33] These scales can be used in children ≥8 years and have demonstrated to (1) accurately approximate ratio scale measurement, (2) to be internally consistent, and (3) to provide a reliable and accurate measure of intensity and unpleasantness separately.[34] Patients completed their current VAS ratings at each visit just prior to device placement and were also asked about their pain intensity and unpleasantness immediately before and after the WL-SPT both pre- and post-PENFS.

Nausea visual analog scale (VAS)[40].: Patients rated their nausea on a visual analog scale similar to the Pain VAS scale anchored with the words “no nausea” versus “most intense nausea.” VAS measures of nausea severity are well correlated with verbal descriptors of nausea.[35] Patients completed the nausea VAS ratings on the same schedule as the Pain VAS.

Fullness rating scale[30]: The Fullness Rating Scale was used where patients chose from 5-line drawings of the human body and each shaded stomach area represented varying degrees of satiety (empty to completely full).

2.4.2 Other measures—GI symptoms were assessed weekly through the Abdominal Pain Index (API)[41] and Nausea Severity Scale (NSS)[42] during treatment and at long-term follow-up. Sleep measures included Pittsburgh Sleep Quality Index (PSQI)[43] and Insomnia Severity Index (ISI)[44] completed before and after treatment and the Patient-Reported Outcomes Measurement Information System (PROMIS) Pediatric Sleep Scales [PROMIS Ped SF v1.0–Sleep Disturbance (SD) 8a–and PROMIS Ped SF v1.0–Sleep-Related Impairment (SRI) 8a][45] completed weekly during treatment. Functioning, somatic, cognitive, and psychological measures included Functional Disability Inventory (FDI),[46] Pain Catastrophizing Scale for Children (PCS-C),[47] and Children’s Somatic Symptoms Inventory (CSSI),[48] which were completed weekly during PENFS and at long-term follow-up. Anxiety and depression were assessed through the Screen for Child Anxiety Related Disorders-Child Report (SCARED)[49] (baseline and long-term), PROMIS Pediatric Anxiety-Short Form Scale,[50] and Pediatric Depression-Short Form scale[51] (weekly during PENFS and long-term). Details of these measures are provided in File S1.

2.3 | 2.5 Statistical analysis

2.3.1 | 2.5.1 Primary aim: Effect of PENFS on abdominal pain and nausea— The resting VAS pain intensity, unpleasantness, and nausea scores captured weekly during PENFS were examined for longitudinal change from baseline before PENFS (Week 0) using linear mixed modeling, accounting for within-subject variability. To examine changes in each VAS measure following PENFS and at various time intervals after WL-SPT, linear mixed modeling was conducted and the main effect for visit and time, and interaction between visit and time were examined with subjects modeled as random effect. Linear mixed modeling was also used to compare total water consumed during WL-SPT from pre- to post-PENFS. All results were presented as least square means and 95% confidence interval.

Prior to the start of the study, we performed a power analysis to detect primary efficacy endpoint difference, that is, VAS pain scale between pre- and post-WL-SPT at Week 4 (visit 5). In Price et al.,[33] they reported mean VAS (also 0–10 scale) at different stimulus temperatures at about 0.8 to 5.2, with SD ranging from 0.3 to 0.8. To power our study, and to detect a VAS difference of 1.0 at a conservative between-subject SD = 1.0, we assumed a moderate correlation within a subject is as 0.5, and then, the SD of a within-subject difference in VAS was 1.0 as well. Under this assumption, for a two-sided paired t-test at 0.05 level, and 80% power, to detect a difference between 4 and 5 in VAS at baseline to week 4, we required a sample size of 10. To test the difference of pre- and post-WL-SPT,

we used SD = 1.0 for the pre- to post-difference in VAS, and SD = 1.0 for the difference between the differences (pre- vs. post-provocation) at baseline and week 4. To detect that difference of 0.7 (between 2 and 1.3), we required a total of 20 patients.

2.3.2 | 2.5.2 Secondary aim: Effect of PENFS on sleep, psychological outcomes, and functioning—Linear mixed modeling was employed to determine the longitudinal change in other pain, nausea, functioning, somatic, and psychological measures from Week 0 to Week 4 and at 6–12 months of follow-up. Subjective sleep measures were similarly assessed from Week 0 to Week 4 and actigraphy measures from Week 1 to Week 4. All results were reported as least square means and standard error.

2.3.3 | 2.5.3 Exploratory aim: Predictors of response to PENFS—To identify variables that predicted treatment outcome, several univariate linear mixed models were developed to associate change in clinical outcomes (VAS pain intensity, pain unpleasantness, and nausea; and FDI) from Week 0 to Week 4 with sleep and psychological measures. The results were presented as beta estimates and standard error.

2.3.4 | 2.5.4 Exploratory aim: Factors mediating the relationship between sleep and abdominal pain—We conducted a mediation analysis, associating VAS pain intensity with PROMIS SD and SRI scores as separate independent variables and anxiety, depression, PCS-C, and CSSI served as mediators in each model, while examining all study visits (Supplement Figure). Mediation models were not developed for VAS unpleasantness and nausea since sleep and psychological measures at baseline did not show any significant association with these outcomes. In each mediation model, “a” indicates the effect of sleep on mediator variable and “b” indicates the effect of each mediator variable on VAS pain intensity as an outcome. The total effect of sleep examined as individual independent variable in each model is a sum of the direct effect of sleep on VAS pain intensity (c’) and indirect effect of sleep on VAS pain intensity through mediating effect (a*b) of each mediator. The proportion of mediation (%) is the indirect effect/total effect. These analyses were done using “mediation” package in R, and the bootstrap method was used to examine whether estimates of mediation effect were statistically significant.[52]

2.3.5 | 2.5.5. Exploratory Aim: Impact of medications and duration of symptoms on baseline measures and changes with PENFS—Changes in subjective sleep assessments, baseline (prior to WL-SPT) pain scores, and other psychological measures were compared using the Wilcoxon rank sum test between those who were on medications and those who were not on any medications. Spearman’s correlation was used to correlate the duration of symptoms with baseline sleep measures, and pain scores, as well as changes from Week 0 to Week 4.

For all analyses except for mediation analysis, SAS version 9.4 (SAS Institute, Cary, NC) was used. For all longitudinal analyses, PROC MIXED procedure was used and few missing data for sleep measures were assumed to be missing at random.

3 | RESULTS

Of the 20 patients, 14 (70%) were females and 19 (95%) were white. The mean age was 14.3 ± 2.2 years, and mean BMI was 24.7 ± 6.7 kg/m^2. Twelve patients were on oral medications for FAPD (50% cyproheptadine, 50% tricyclic antidepressants, and 16% selective serotonin reuptake inhibitors). Eighteen patients met criteria for FD [11 had postprandial distress syndrome (PDS) and 7 epigastric pain syndrome], two had IBS and three FAP-NOS. One patient with IBS had overlapping PDS. None of the patients had a diagnosed sleep disorder. The average symptom duration before treatment was 27.5 months (7–83 months). Screening laboratories like complete blood count and comprehensive metabolic panel; serum inflammatory markers, fecal calprotectin, upper endoscopy/colonoscopy, and gastric emptying scans were available for 90%, 60%, 55%, 90%, and 75% of patients, respectively. All investigations were essentially normal except one patient had delayed gastric emptying. One patient discontinued PENFS after two weeks due to development of acute cholecystitis during treatment.

3.1 | Impact of PENFS on abdominal pain and nausea (Aim 1)

3.1.1 | Resting and self-reported symptom measures—The impact of PENFS on abdominal pain and nausea was assessed with VAS and validated surveys (Abdominal Pain Index, API; Nausea Severity Scale, NSS). Resting VAS ratings for pain unpleasantness ($p = 0.03$) were reduced after four weeks of PENFS therapy. Pain intensity had a trend for improvement ($p = 0.06$), but VAS nausea did not change ($p = 0.10$). Scores on the API significantly improved after therapy ($p < 0.0001$). There was a trend for improvement of nausea on the NSS after treatment ($p = 0.07$; Table 2).

3.1.2 | Evoked symptom measures—All patients completed WL-SPT before and following PENFS (Figure 1). We examined whether PENFS would reduce pain intensity, unpleasantness, and nausea during WL-SPT. First, we examined the effect of study visit (pre- and post-PENFS) and timing of WL-SPT. The evoked pain intensity [LS Means (95%CI)] reduced significantly from pre- to post-PENFS [2.05 (1.04–3.07) to 1.56 (0.55–2.58), $p < 0.01$], respectively. It also reduced from baseline to 10 mins post-WL [1.89 (0.86–2.92) to 1.58 (0.55–2.61), $p = 0.049$], respectively. Subsequently, we examined the interaction between the study visit and the timing of WL-SPT. VAS pain intensity before PENFS increased immediately post-WL-SPT but reduced at 5 and 10 min to pre-baseline level. After PENFS, baseline VAS pain intensity was significantly lower compared with pre-treatment ($p = 0.03$). Pain intensity immediately post WL-SPT was also lower compared to pre-treatment ($p = 0.004$). It was lower compared to pre-treatment at 5 and 10 min but was not statistically significant ($p = 0.15$ and $p = 0.48$, respectively). Thus, PENFS appeared to blunt the increase in VAS pain intensity seen immediately after WL-SPT.

The effects of PENFS visit or timing of WL-SPT on pain unpleasantness were not significant ($p = 0.24$ and 0.34, respectively). When examining the interaction between visit and time, pain unpleasantness showed a different profile as ratings decreased after WL-SPT pre-PENFS but increased post-PENFS. Baseline VAS pain unpleasantness was lower after treatment compared to before ($p = 0.05$) but unpleasantness following WL-SPT did not

differ with treatment ($p = 0.51$, $p = 0.86$ and $p = 0.88$ immediately after WP-SPT and at 5 and 10 min, respectively). Even though unpleasantness scores were higher following WL-SPT post-PENFS, they were still lower compared with baseline pre-treatment.

Lastly, for VAS nausea scores [LS Means (95%CI)], the effect of PENFS visit was significant and the scores reduced from pre- to post-PENFS [1.00 (0.39–1.62) to 0.63 (0.014–1.25), $p < 0.01$], respectively. The effect of treatment on nausea scores (baseline to 10 min post-WL-SPT) was not significant [0.86 (0.23–1.50) to 0.67(0.033–1.31), $p = 0.31$], respectively. Examining visit and time effect interactively, VAS nausea showed a similar response as VAS pain intensity. Before PENFS, it increased immediately following WL-SPT but reduced to pre-baseline levels at 5 and 10 min. After PENFS treatment, baseline VAS nausea showed a trend for improvement compared with pre-treatment ($p = 0.09$). VAS nausea scores immediately after WL-SPT were lower compared with pre-treatment ($p = 0.02$). They continued to be lower at 5 and 10 min compared to pre-treatment but were not statistically significant ($p = 0.16$ and $p = 0.55$, respectively). Thus, PENFS treatment appeared to blunt the increase in VAS nausea seen post-WL-SPT.

Total water intake during WL-SPT did not differ before and after PENFS (474.5±56.4 vs 413.7±58.4, $p = 0.16$). Thus, the drop in post-WL-SPT VAS pain intensity and nausea after PENFS may directly represent an effect of the treatment since the amount of water did not change.

3.2 | Impact of PENFS on sleep and psychological functioning (Aim 2)

3.2.1 | Resting and self-reported sleep before and after PENFS therapy—

To examine the impact of PENFS on self-reported sleep difficulties, patients completed surveys about sleep quality (PSQI), insomnia symptoms (ISI), sleep disturbance (PROMIS-SD), and sleep-related impairments (PROMIS-SRI). The baseline PSQI and ISI scores were 8.7 (±4.3) and 10.8 (±6.5), respectively. Both scored higher than those reported in healthy adolescents[53–56] and suggest that patients were experiencing poor sleep quality and higher insomnia symptoms. The mean PROMIS-SD and SRI T-scores were 60.3 (±9.6) and 59.1 (±10.5), respectively. Both scores were higher than reported in historic healthy controls[57,58] and slightly worse than patients with sleep disorders in chronic illnesses and neurodevelopmental disorders.[58]

Patients reported improvements in sleep following PENFS. While general sleep quality (PSQI, $p = 0.08$) and insomnia symptoms (ISI, $p = 0.06$) showed a trend for improvement, patients reported a significant decrease in sleep-related impairments (PROMIS-SRI, $p = 0.005$) and disturbances (PROMIS-SD, $p = 0.01$, Figure 2) following PENFS. Daily ratings of sleep quality, which coincided with the collection of actigraphy during weeks 1 through 4 of the study, did not change during treatment ($p = 0.53$), while numeric pain ratings improved ($p = 0.04$).

3.2.2 | Actigraphic sleep-wake patterns during PENFS therapy—

Sleep onset latency showed a significant decrease from week 1 to week 4 of PENFS ($p = 0.03$), which was largest during week 3 ($p = 0.01$). Other variables, including time in bed, total sleep time,

WASO, sleep efficiency, and sleep onset variability, did not change during treatment (Figure 3).

3.2.3 | Physical, psychological, and somatic measures before and after PENFS therapy—

Disability (FDI) improved from baseline to week 4 ($p = 0.04$). Similar improvements in catastrophizing (PCS-C, $p = 0.0004$), somatic ($p = 0.01$), and GI ($p = 0.01$) subscales of the CSSI, and anxiety (PROMIS anxiety, $p = 0.03$, and SCARED, $p = 0.02$) but not depression (PROMIS Depression, $p = 0.14$) were observed over the course of PENFS (Table 2).

3.2.4 | Sustained improvements in self-reported GI Symptoms, Physical and Psychological Functioning, and Somatic Symptoms—

Following PENFS, API, NSS, FDI, PCS-C, CSSI, and SCARED continued to show sustained improvements at 6–12 months follow-up ($p < 0.05$), PROMIS anxiety showed a trend for improvement ($p = 0.05$), while depression scores did not change (Table 2).

3.3 | Exploratory analysis

3.3.1 | Association of baseline sleep and psychological measures with improvements in GI symptoms and disability from week 0 to week 4—

High baseline catastrophizing (PCS-C) and overall somatic (CSSI) scores were positively associated with lower reductions in resting VAS pain intensity from week 0 to week 4 ($p = 0.01$ and 0.04, respectively; Table 3). Similarly, patients who had high baseline PROMIS anxiety and depression scores showed lower reductions in FDI from week 0 to week 4 ($p = 0.04$ and 0.05, respectively). None of the baseline measures showed significant association with changes in pain unpleasantness or nausea.

3.3.2 | Psychological and somatic measures as mediators of relationship between pain intensity and self-reported sleep—

Anxiety (PROMIS), depression (PROMIS), pain catastrophizing (PCS-C), and somatic complaints (CSSI) directly and indirectly mediated the effect of sleep on abdominal pain (Table 4 and Figure 4). The direct effect of sleep disturbance (PROMIS-SD) on VAS pain intensity was significant with each psychological and somatic measure as mediator (all p's < 0.05). The indirect effect of each mediator variable was also significant, with 41% of sleep disturbance effect on pain mediated by PROMIS anxiety, 33% by PROMIS depression, 40% by PCS-C, and 27% by CSSI. Associating sleep impairment (PROMIS-SRI) with VAS pain intensity, the direct effect of all mediators was not significant. However, the indirect effects of PROMIS anxiety, PROMIS depression, PCS-C, and CSSI on the relationship between sleep impairment and pain intensity were significant and the proportion of mediation effect were 90%, 77%, 66%, and 65%, respectively.

3.3.3 | Impact of medications and duration of symptoms on baseline measures and changes with PENFS—

Patients who were on medications to treat FAPD ($n = 12$) had worse baseline ISi and PROMIS-SRI scores than those who were not on medications ($n = 8$, $p = 0.04$, and $p = 0.01$, respectively). Note that we did not account for multiple comparisons. There were no differences in outcomes between the two groups

with PENFS treatment. Similarly, there was no correlation between duration of symptoms with sleep and anxiety measures at baseline as well as changes with PENFS (Supporting information 2 and 3).

4 | DISCUSSION

It is known that PENFS is associated with improvements in pain and functional disability in adolescents with FAPDs. This study extends previous studies by evaluating changes in visceral sensitivity using a water load task, actigraphic and subjective sleep measures, and other psychological factors. We show for the first time that PENFS is associated with changes in mechanosensitivity and improvements in sleep, pyschological factos like catastrophizing, and somatic complaints. The changes in abdominal pain, nausea, and psychological measures were also sustained for 6–12 months post-treatment.

Our primary aim was to determine changes in abdominal pain and nausea during PENFS. Resting VAS pain unpleasantness decreased significantly following PENFS, while there was a trend for improvement in pain intensity. In contrast, in a randomized trial assessing changes in abdominal pain with treatment of anxiety, minimal changes in VAS pain intensity have been reported in the standard medical care control group, suggesting it to be the natural trend over time for that measure.[6] Abdominal pain on the API significantly improved in our study, while there was a trend for improvement of nausea severity on the NSS after four weeks of PENFS. While the first RCT on PENFS used questionnaires,[31] we utilized visual analog scales and symptom provocation in addition to questionnaires and assessed different dimensions of pain.

Evoked pain can mimic postprandial symptoms and is considered a better indicator of patient symptoms.[30] In the present investigation, pain followed a unique time course during WL-SPT. VAS pain intensity and nausea scores increased immediately after WL-SPT, plateaued at 5 min and declined to pre-baseline levels thereafter. In contrast, pain unpleasantness was highest at baseline immediately prior to WL-SPT and then declined thereafter. There may be an expectation effect of increase since baseline VAS measures were obtained immediately before WL-SPT and device placement at each visit. Such an expectation effect has been described in functional magnetic resonance imaging studies in healthy volunteers. In addition, negative expectations amplify pain processing in neural networks mediating visceral pain, and modify the activity of the pain modulation areas by emotional and cognitive factors.[59] The high levels immediately after but declining at 5 and 10 min after WL-SPT could be partly explained by the exponential rate of emptying of liquids from the stomach without a lag phase.[60]

VAS pain intensity and nausea were lower immediately post WL-SPT after PENFS when compared to baseline. However, water intake did not change pre and post WL-SPT. Our findings support prior literature on the mechanisms of action of PENFS. Increased pain after WL-SPT has been described in adolescents with functional dyspepsia who had impaired sympathovagal tone.[61] Another study has suggested that patients with vagal insufficiency were most likely to respond to PENFS.[34] Thus, it could be speculated that PENFS may be decreasing pain and nausea post-WL-SPT by correcting the sympathovagal balance.

Interestingly, there was no change in pain unpleasantness after PENFS. This differential effect on the dimensions of pain needs further investigation.

Our secondary aim was to determine changes in sleep during treatment. We found poor sleep quality and a higher incidence of baseline insomnia, sleep disturbances, and sleep-related impairment despite 60% of patients being on daily medications for pain, which are known to improve sleep. This is similar to previous reports of poor sleep quality and insomnia in chronic pain conditions[19,20,23] and children with functional abdominal pain.[9–12] We found that patients who were on medications including neuromodulators had worse baseline insomnia severity and sleep-related impairment compared to those not on medications. While this appears contradictory, it is often seen in clinical practice as well. It is hard to tease out if these differences are due to the medications themselves or if the patients on these medications have more severe symptoms that may have a bigger impact on their life. There was a robust improvement in self-reported sleep disturbance and sleep-related impairment on the pediatric PROMIS measures and a trend for improvement in sleep quality and insomnia symptoms over four weeks. Differences across these measures could be due to the timeframe anchored to each survey. Compared with the PSQI and ISI (past month), the PROMIS measures (past week) might have captured weekly improvements in sleep during treatment. Actigraphy showed poor sleep efficiency and higher sleep onset latency, sleep onset variability, and Wake After Sleep Onset (WASO) in patients with FAPD compared with that reported in healthy peers.[62] Decreased sleep efficiency and increased WASO have been reported in other chronic pain conditions.[19] However, sleep onset latency was the only sleep/wake measure that was decreased while other variables did not change. It is hard to discern whether PENFS directly targets sleep pathways to improve sleep, consequently improving pain and other clinical parameters versus improvements in pain lead to improved sleep. In past studies, the strongest temporal association is in favor of sleep deficiency impacting next day pain.[63,64] The dorsal motor nucleus and nucleus ambiguous that receive parasympathetic input are located close to and regulated by the solitary tract nucleus, which functions as the hindbrain sleep center. Parasympathetic activity before falling asleep has shown to regulate the sleeping drive.[33] This could partially explain the improvement in sleep onset latency with PENFS treatment. Thus, changes in sleep with PENFS could be attributed to the direct effect on the sleep-vagal axis or secondary to improved psychological well-being.

Finally, we sought to assess changes in functional disability and psychological functioning with PENFS. Functional disability improved throughout treatment and at long-term follow-up. Anxiety scores improved post-PENFS, while there was no change in depression. In adults, GI-specific anxiety correlates with IBS severity and is regarded an important psychosocial variable underlying visceral pain sensitivity, hypervigilance, and maladaptive coping.[65] Improvements in anxiety after PENFS were likely secondary to improved GI symptoms. However, improvements in anxiety through direct effects on specific CNS pathways cannot be excluded. Preclinical studies have demonstrated modulation of neuronal amygdalar activity as a potential mechanism of action of PENFS.[32] Theoretically, this could result in clinical benefits, particularly as it relates to anxiety.[32] In our exploratory analysis, we found anxiety and depression to mediate the effect of sleep impairment on pain intensity

by about 90 and 77%, respectively. Prior studies have reported about 40% of the total effect of sleep quality on pain intensity to be explained through anxiety and depression.[66]

Adult and pediatric studies have implicated somatization and pain catastrophizing to mediate the relationship between anxiety and IBS symptom severity.[15,16] Pain catastrophizing is the irrational expectation of the worst outcome in response to an actual or anticipated painful event while somatization is physiological symptoms that cannot be explained medically.[15,16] They also affect disability and other outcomes in children with functional abdominal pain.[17,18] Patients in our cohort exhibited somatization and catastrophizing consistent with previously described literature. We noted marked improvements in these variables with PENFS that were sustained at long-term follow-up. A similar potential mechanism involving modulation of the amygdala could be responsible for processing emotional responses to pain, including catastrophizing.[67] Thus, PENFS can potentially affect the neural axis at multiple levels including afferent processing and effects on supraspinal affective processes relative to pain like somatization, catastrophizing, and anxiety.

In assessing predictors of response to PENFS therapy, those with higher pain catastrophizing and somatization had lesser reduction in VAS pain scores, while those with high anxiety had lesser improvements in functioning. It is possible that patients with worse psychological state may need a longer duration of treatment to notice improvements in pain and nausea, but this needs further investigation.

Our study had some inherent limitations including a small sample size, a heterogeneous population including FD and IBS, and lack of a control/sham group. However, these factors were mitigated by a within-subject design that is intrinsically more powerful than a between-subject design. We did not have baseline actigraphy data prior to PEN FS. This would have necessitated additional visits, which would further add challenges to participant recruitment.

To conclude, we demonstrated improvements in pain intensity and nausea through visual analog scales and validated questionnaires. We also showed improvements in gastric mechanosensitivity through water load task. To our knowledge, this is the first study to assess actigraphic sleep variables in adolescents with FAPD and to determine sleep changes with PENFS. Few studies have assessed changes in sleep with treatment for chronic pain and none in children with functional abdominal pain. Disability, pain catastrophizing, somatization, and anxiety reduced after four weeks of PENFS and effects were sustained at 6–12 months post-treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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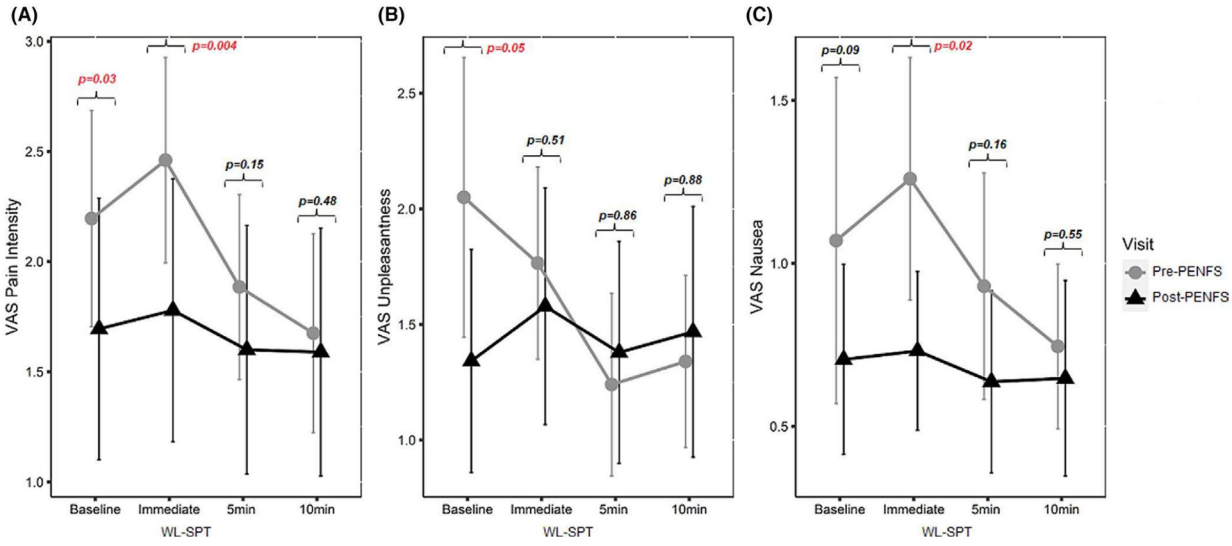

FIGURE 1.

Water Load Symptom Provocation Task (WL-SPT) before and following Percutaneous Electrical Nerve Field Stimulation (PENFS). Pain intensity, unpleasantness, and nausea visual analog scale (VAS) scores were recorded before, immediately after, at 5 and 10 min of the WL-SPT compared with pre-baseline scores before and after PENFS. *p* values <0.05 indicate statistical significance

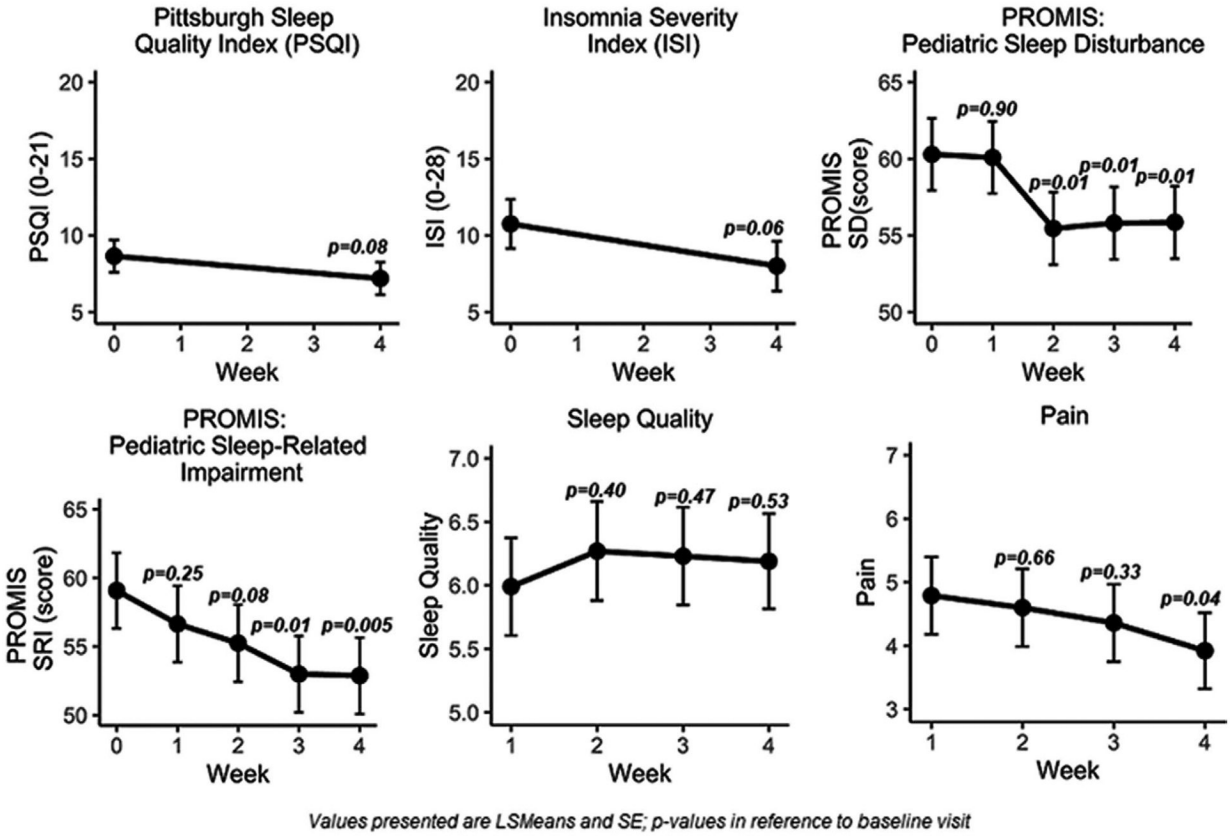

FIGURE 2.

Changes in subjective sleep and sleep-related measures with PENFS therapy. This figure shows changes in validated sleep measures like sleep quality, insomnia severity, sleep disturbance, sleep-related impairment, and daily diary variables including numeric ratings of sleep quality and pain from baseline to the end of the 4 weeks of PENFS therapy. *p* values < 0.05 indicate statistical significance

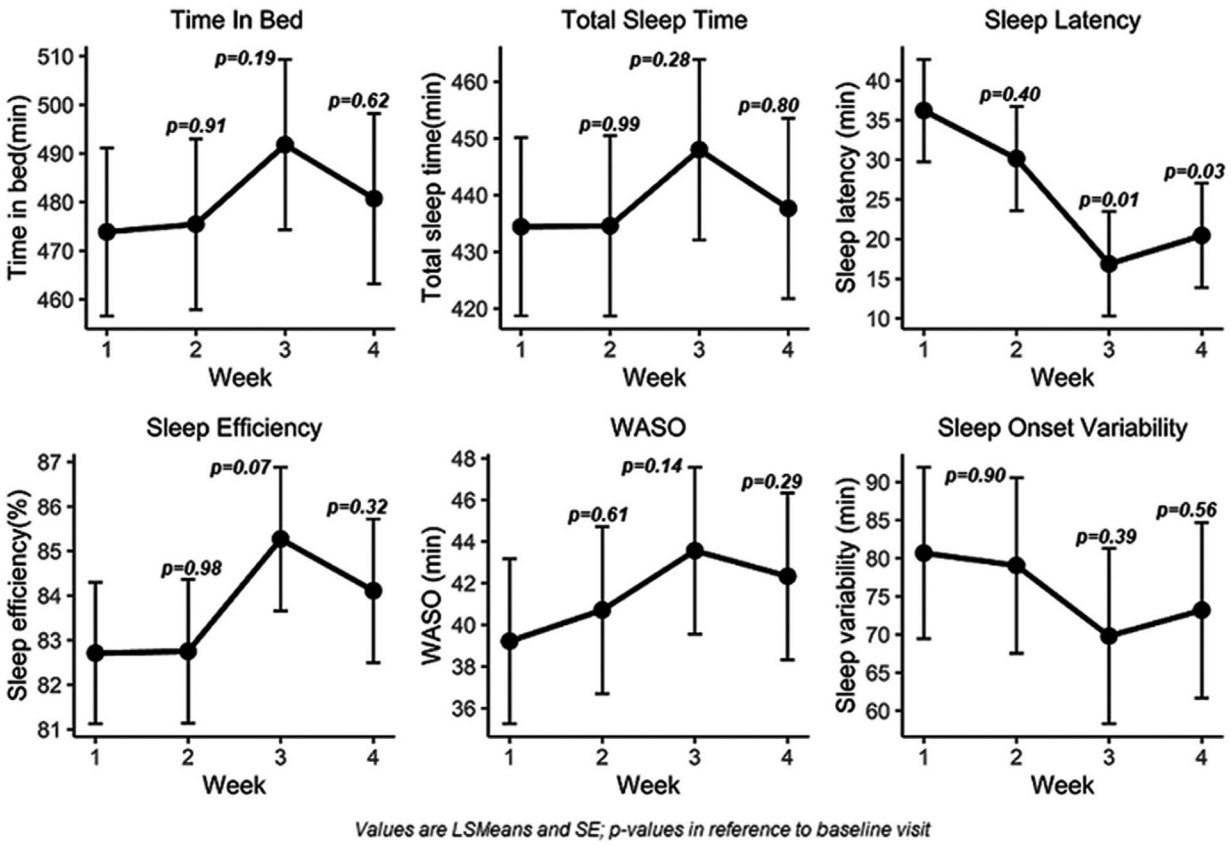

FIGURE 3.

Changes in actigraphy variables with PENFS therapy. This figure shows changes in actigraphic sleep indices of total sleep time, time in bed, sleep latency, sleep efficiency, Wake After Sleep Onset (WASO), and sleep onset variability after first PENFS device placement for 4 weeks. p values < 0.05 indicate statistical significance

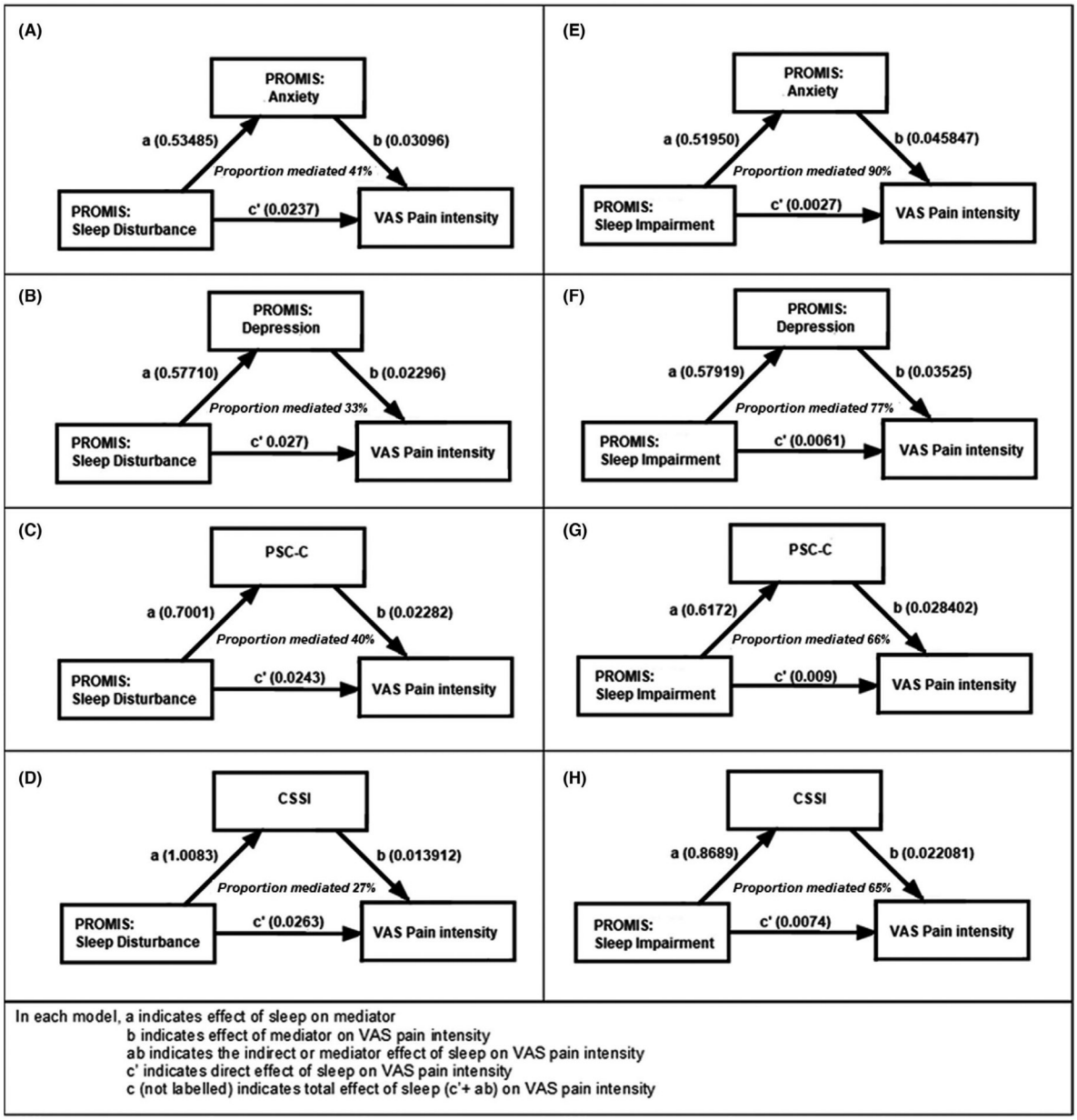

FIGURE 4.

Psychological parameters mediating sleep and abdominal pain. This figure shows mediation analyses associating visual analog scale (VAS) pain intensity with sleep disturbance and sleep-related impairment as separate independent variables, while anxiety, depression, pain catastrophizing (PCS-C), and somatization (CSSI) as mediators in each model

TABLE 1

Timeline of measures

	Pre-first PENFS Placement Visit	Rest of PENFS Placement (Weekly)	Post-PENFS Visit	Follow-up
GI Symptom Characteristics				
Resting Pain VAS	X	X	X	
Resting Nausea VAS	X	X	X	
Nausea Severity Scale (NSS)	X	X	X	X
Abdominal Pain Index (API)	X	X	X	X
Physical Functioning				
Functional Disability Inventory (FDI)	X	X	X	X
Sleep				
Pittsburgh Sleep Quality Index (PSQI)	X		X	
Insomnia Severity Index (ISI)	X		X	
PROM IS Ped SF vl.O–Sleep Disturbance 8a–Child (PROMIS-SD)	X	X	X	
PROM IS Ped SF vl.O–Sleep-Related Impairment 8a–Child (PROMIS-SRI)	X	X	X	
Sleep Diary	X	X	X	
Psychological Functioning				
PROMIS Pediatric Depression–short-form scale	X	X	X	X
PROMIS Pediatric Anxiety–short-form scale	X	X	X	
Pain Catastrophizing for Children (PSC-C)	X	X	X	X
Screen for Child Anxiety-Related Emotional Disorders (SCARED)	X		X	X
Somatic				
Child Somatic Symptoms Inventory (CSSI)	X	X	X	X

Abbreviations: PENFS, Percutaneous Electrical Nerve Field Stimulation; VAS, Visual Analog Scale.

TABLE 2

Effects on symptoms before, during, and after PENFS

		Penfs						
Parameters	**Baseline**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	***p* value[§]**	**Follow-up**	***p* value[€]**
GI Symptoms								
Resting VAS								
Pain Intensity	2.2 ± 0.52	1.72 ± 0.52	1.75 ± 0.53	1.73 ± 0.53	1.61 ± 0.53	0.06	~	~
Pain Unpleasantness	2.05 ± 0.5	1.21 ±0.5	1.33 ± 0.51	1.28 ± 0.51	1.28 ± 0.51	0.03	~	~
Nausea	1.07 ± 0.44	0.41 ± 0.44	0.61 ± 0.44	0.74 ± 0.44	0.68 ± 0.44	0.10	~	~
API	2.84 ± 0.25	2.39 ± 0.25	2.08 ± 0.26	2.05 ± 0.26	1.9 ± 0.26	<0.0001	1.39 ± 0.27	<0.0001
NSS	1.78 ± 0.25	1.66 ± 0.25	1.14 ± 0.25	1.36 ± 0.25	1.33 ± 0.25	0.07	0.90 ± 0.27	0.001
Physical Functioning								
FDI	18.95 ± 3.06	15.3 ± 3.06	15.12 ± 3.07	15.07 ± 3.07	15.54 ± 3.07	0.04	10.09 ± 3.14	<0.0001
CSSI (Somatic symptoms)	28.25 ± 3.81	21 ±3.81	20.61 ± 3.85	20.04 ± 3.85	20.4 ± 3.85	0.01	17.8 ± 4.05	0.002
CSSI (GI symptoms)	9.9 ± 1.1	7.65 ± 1.1	7.4 ± 1.12	6.92 ± 1.12	7.19 ± 1.12	0.01	6.14 ± 1.2	0.002
Psychological Functioning								
PCS-C	23.85 ± 3.24	19.85 ± 3.24	18.08 ± 3.27	16.5 ± 3.27	15.4 ± 3.27	0.0004	14.88 ± 3.42	0.001
SCARED	22.5 ± 4.3	~	~	~	17.5 ± 4.3	0.02	16.9 ± 4.4	0.03
PROMIS Anxiety	51.87 ± 2.27	48.28 ± 2.27	48.85 ± 2.28	48.03 ± 2.28	48.72 ± 2.28	0.03	48.87 ± 2.35	0.05
PROMIS Depression	48.6 ± 2.4	45.1 ± 2.4	46.27 ± 2.42	45.73 ± 2.42	46.78 ± 2.42	0.14	47.85 ± 2.49	0.63

Note: API, Abdominal Pain Index; CSSI, Children's Somatic Symptoms Inventory; FDI, Functional Disability Inventory; NSS, Nausea Severity Scale; PCS-C, Pain Catastrophizing Scale for Children; PENFS, Percutaneous Electrical Nerve Field Stimulation; SCARED, Screen for Child Anxiety-Related Emotional Disorders; VAS, Visual Analog Scale.

All values are LS Means and SE;

[§] p for Week 4 vs. Week 0;

[€] p for long-term follow-up vs. Week 0

TABLE 3

Baseline predictors of change in VAS measures and FDI

	VAS Pain Intensity		VAS Pain Unpleasantness		VAS Nausea		FDI	
Individual Predictor	**β-estimate ±SE**	***p* value**	**β-estimate ±SE**	***p* value**	**β-estimate ±SE**	***p* value**	**β-estimate ±SE**	***p* value**
Sleep								
PSQI	0.034 ± 0.088	0.71	−0.002 ± 0.137	0.99	0.039 ± 0.088	0.66	0.082 ± 0.586	0.89
ISI	0.021 ± 0.058	0.73	−0.061 ± 0.088	0.50	−0.028 ± 0.058	0.63	0.145 ± 0.382	0.71
PROMIS-SD	0.011 ± 0.039	0.78	−0.02 ± 0.06	0.75	−0.029 ± 0.038	0.46	0.114 ± 0.255	0.66
PROMIS-SRI	0.004 ± 0.035	0.91	−0.032 ± 0.053	0.55	0.003 ± 0.035	0.93	0.121 ± 0.229	0.61
Psychological and Somatic								
PCS-C	0.082 ± 0.028	0.01	0.046 ± 0.051	0.38	−0.029 ± 0.033	0.40	0.128 ± 0.223	0.57
CSSI	0.048 ± 0.021	0.04	0.032 ± 0.037	0.40	−0.005 ± 0.024	0.85	−0.059 ± 0.161	0.72
PROMIS Anxiety	0.064 ± 0.042	0.14	0.02 ± 0.068	0.77	−0.045 ± 0.043	0.31	0.574 ± 0.259	0.04
PROMIS Depression	0.072 ± 0.036	0.06	−0.014 ± 0.061	0.83	−0.011 ± 0.04	0.78	0.505 ± 0.234	0.05
SCARED	0.029 ± 0.022	0.22	−0.036 ± 0.035	0.32	−0.021 ± 0.023	0.36	0.193 ± 0.147	0.21

Note: Abbreviations: CSSI, Children's Somatic Symptoms Inventory; FDI, Functional Disability Inventory; ISI, Insomnia Severity Index; PCS-C, Pain Catastrophizing Scale for Children; PROMIS-SD, PROMIS Sleep Disturbance; PROMIS-SRI, Sleep-Related Impairment; PSQI, Pittsburgh Sleep Quality Index; SCARED, Screen for Child Anxiety Related Emotional Disorders; VAS, Visual Analog Scale.

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TABLE 4

Mediation of Psychological Factors and Pain Intensity by Sleep Disturbance and Impairment

	VAS pain intensity—Sleep disturbance				VAS pain intensity - Sleep impairment			
Mediator	**Estimate**	**95%LCL**	**95%UCL**	***p* value**	**Estimate**	**95%LCL**	**95%UCL**	***p* value**
PROMIS Anxiety								
Indirect Effect of Sleep	0.0166	0.0042	0.03	0.010 **	0.0238	0.0076	0.04	0.0040 **
Direct Effect of Sleep	0.0237	0.0043	0.04	0.017 *	0.0027	−0.0175	0.02	0.812
Total Effect	0.0403	0.0255	0.06	<2e-16 ***	0.0266	0.0140	0.04	0.0004 ***
Proportion Mediated	0.4110	0.1012	0.86	0.010 **	0.8969	0.2679	1.94	0.0040 **
PROMIS Depression								
Indirect Effect of Sleep	0.0133	0.0013	0.03	0.031 *	0.0204	0.0057	0.04	0.0060 **
Direct Effect of Sleep	0.0270	0.0090	0.05	0.004 **	0.0061	−0.0139	0.02	0.5284
Total Effect	0.0403	0.0260	0.06	<2e-16 ***	0.0266	0.0143	0.04	0.0004 ***
Proportion Mediated	0.3289	0.0287	0.70	0.031 *	0.7688	0.2062	1.75	0.0064 **
PCS-C								
Indirect Effect of Sleep	0.0160	0.0072	0.03	<2e-16 ***	0.0175	0.0082	0.03	<2e-16 ***
Direct Effect of Sleep	0.0243	0.0095	0.04	0.002	0.0090	−0.0052	0.02	0.19
Total Effect	0.0403	0.0258	0.06	<2e-16 ***	0.0266	0.0148	0.04	<2e-16 ***
Proportion Mediated	0.3967	0.1806	0.68	<2e-16 ***	0.6601	0.3163	1.27	<2e-16 ***
CSSI								
Indirect Effect of Sleep	0.0097	0.0009	0.02	0.0300 *	0.0136	0.0049	0.03	0.0004 ***
Direct Effect of Sleep	0.0263	0.0074	0.05	0.0048 **	0.0074	−0.0132	0.02	0.4732
Total Effect	0.0360	0.0203	0.05	<2e-16 ***	0.0210	0.0064	0.03	0.0060 **
Proportion Mediated	0.2706	0.0242	0.68	0.0300 *	0.6490	0.1933	2.47	0.0064 **

Note: CSSI, Children's Somatic Symptoms Inventory; PCS-C, Pain Catastrophizing Scale for Children; VAS, Visual Analog Scale.