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THERAPEUTIC OUTCOMES OF DRY NEEDLING COUPLED WITH INTRAMUSCULAR ELECTRIC STIMULATION IN PATIENTS WITH FIBROMYALGIA SYNDROME

RESULTADOS TERAPÊUTICOS DA ACUPUNTURA SECA COMBINADA COM ESTIMULAÇÃO ELÉTRICA INTRAMUSCULAR EM PACIENTES COM SÍNDROME DA FIBROMIALGIA

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Abstract

Objective: To determine whether dry needling combined with intramuscular electrical stimulation (DN+IMS) results in different effects on pain, pressure pain threshold, sleep quality, mood, and fatigue compared with dry needling (DN) alone in fibromyalgia. Methods: This assessor-blinded randomized controlled trial was conducted at a tertiary hospital in Pakistan. Seventy-eight adults with fibromyalgia (18–60 years) were randomized to DN+IMS (n=39) or DN alone (n=39). Both groups received weekly myofascial trigger point needling for 4 weeks and additionally received standard treatment; the DN+IMS group also received biphasic electrical stimulation (2–4 Hz, 20 min). Outcomes were assessed at baseline and weeks 2, 4, and 8 using

Resumo

Objetivo: Determinar se a agulhagem a seco combinada com estimulação elétrica intramuscular (DN+IMS) produz efeitos diferentes sobre a dor, o limiar de dor à pressão, a qualidade do sono, o humor e a fadiga, em comparação com a agulhagem a seco (DN) isolada na fibromialgia. Métodos: Este ensaio clínico randomizado e controlado, com avaliador cego, foi realizado em um hospital terciário no Paquistão. Setenta e oito adultos com fibromialgia (18–60 anos) foram randomizados para o grupo DN+IMS (n=39) ou apenas DN (n=39). Ambos os grupos receberam agulhamento semanal nos pontos-gatilho miofasciais por 4 semanas e, adicionalmente, receberam tratamento padrão; o grupo

the Numeric Pain Rating Scale (primary outcome), pressure pain threshold, Pittsburgh Sleep Quality Index, Hospital Anxiety and Depression Scale, and Multidimensional Fatigue Inventory-20. Intention-to-treat analyses used multiple imputation by chained equations (M=50) and linear mixed models. Results: DN+IMS showed larger pain reductions at weeks 2–8 (β −1.00 to −1.26; p≤0.020) and greater increases in pressure pain threshold during treatment (β 0.35–0.46; p<0.001). Sleep quality and mood improved at weeks 4 and 8 (p≤0.010), with fatigue improvements were selective and limited to specific domains/timepoints. Conclusions: Adding IMS to DN improved pain, sleep quality, and mood outcomes in fibromyalgia.

Keywords: Dry Needling. Electrical Stimulation Therapy. Fatigue. Fibromyalgia. Pain Measurement.

DN+IMS também recebeu estimulação elétrica bifásica (2–4 Hz, 20 min). Os resultados foram avaliados no início do estudo e nas semanas 2, 4 e 8 utilizando a Escala Numérica de Avaliação da Dor (desfecho primário), o limiar de dor à pressão, o Índice de Qualidade do Sono de Pittsburgh, a Escala Hospitalar de Ansiedade e Depressão e o Inventário Multidimensional de Fadiga-20. As análises por intenção de tratar utilizaram imputação múltipla por equações encadeadas (M=50) e modelos lineares mistos. Resultados: O grupo DN+IMS apresentou maiores reduções da dor nas semanas 2–8 (β −1,00 a −1,26; p ≤ 0,020) e maiores aumentos no limiar de dor à pressão durante o tratamento (β 0,35–0,46; p < 0,001). A qualidade do sono e o humor melhoraram nas semanas 4 e 8 (p ≤ 0,010), com melhorias na fadiga sendo seletivas e limitadas a domínios/momentos específicos. Conclusões: A adição da IMS à DN melhorou os resultados relativos à dor, à qualidade do sono e ao humor na fibromialgia.

Palavras-chave: *Agulhamento a Seco. Terapia de Estimulação Elétrica. Fadiga. Fibromialgia. Medição da dor.*

1 BACKGROUND

Fibromyalgia (FM) is a chronic disorder having characterized by widespread musculoskeletal pain, fatigue, sleep disturbances, and psychological symptoms. It affects around 2%–4% of the global population, with more prevalence in women [1-3]. The complex pathophysiology, including central sensitization, nociceptive systems, and myofascial trigger points, contributes to disability and a poor quality of life [4, 5]. Although pharmacological interventions, physical exercise, cognitive behavioral therapy, and patient education have shown moderate effects, there remains a need to search for effective non-pharmacological interventions [6-9]. Dry needling (DN), in which fine needles are inserted into MTrPs to produce a local twitch response, holds promise for the management of FM. Pain reduction occurs through the modulation of peripheral and central sensitization and the improvement of pressure pain thresholds (PPT) [3, 10-12]. A 2022 systematic review and meta-analysis of 13 randomised controlled trials (RCTs) found that, based on moderate certainty evidence, pain intensity was reduced in patients

with FM following DN, with a mean difference of -1.53 on the 95% CI -2.29 to -0.78, and quality of life was improved, and on low certainty evidence, fatigue, anxiety, depression, and sleep were also improved [13]. More recent RCTs have reinforced the evidence that DN reduces pain more than stretching in the management of FM, with a 3.2-point reduction on the Visual Analog Scale compared to 1.8-point reduction for stretching, at 4 weeks [14], and that pain and function are improved in patients with FM and high pain catastrophizing, though the benefits are not sustained in the long term, [15-17]. These studies reinforce the potential benefits of DN in the management of FM, including its potential role in the multimodal management of the condition, alongside other treatments [18, 19].

The therapeutic effects of DN are increased by the addition of intramuscular electrical stimulation, referred to as DN+IMS, which addresses the effects of peripheral and central sensitization. DN+IMS acts on MTrPs by decreasing spontaneous electrical activity and the release of pain mediators, such as substance P and CGRP, and activating the segmental inhibition response through the gate control mechanism by stimulating the A-delta and C nerve fibers [3, 20]. Low-frequency electrical stimulation in the range of 2-10 Hz increases the release of endogenous opioids such as beta-endorphins and enkephalins in the periaqueductal grey and the rostral ventromedial medulla, increases serotonin and norepinephrine levels, and increases muscle blood flow, reducing ischemia and tissue [2, 19, 21, 22]. Direct evidence of benefit in FM does not exist in the body of evidence on DN+IMS, though the evidence on EA does indicate potential benefits, including improvements in pain thresholds, as demonstrated in a 1992 RCT, in which there was a 70% increase in pain thresholds, and improvements in quality of life [23, 24]. These studies are limited by small samples and heterogeneous protocols, leaving DN+IMS's efficacy in FM untested [3, 5, 13, 25].

Considering the high burden of FM and the fact that there are no RCTs that have assessed the efficacy of DN+IMS in FM patients, the current study was designed to fill this gap by comparing the efficacy of DN+IMS and DN in FM patients with standard physiotherapy treatment in both groups. The study was designed to assess the efficacy of DN+IMS in comparison to DN in terms of the improvement in pain intensity and fatigue, as well as improvements in PPT, sleep quality, and mood in FM patients.

2 METHODS

The study design used in this study is a randomized, parallel group clinical trial, and the study setting for this clinical trial was a tertiary care hospital (University of Lahore Hospital), Lahore, Pakistan, from June 25, 2024, to August 31, 2025, aiming to compare the effectiveness of dry needling with electrical stimulation and dry needling alone in patients with fibromyalgia. This study was approved by the institutional review board of the faculty of allied health sciences, the University of Lahore, and this study adheres to the principles of the Declaration of Helsinki and has been registered in the Iranian registry of clinical trials, IRCT20240125060803N1. The sample size calculation for this study was done a priori, and the pilot study included 30 patients with fibromyalgia, and the primary outcome for this study was Numeric Pain Rating Scale, NPRS [3, 4, 14]. Although unpublished pilot data from our institution (n=30) suggested d≈0.75, we powered the trial conservatively at d=0.68 (two-sided $\alpha = 0.05$, 80% power, 1:1 allocation), using G*Power software (version 3.1.9.7; Heinrich-Heine-Universität Düsseldorf, Germany) to calculate the required sample size. This yielded 35 participants per group (N = 70). To account for an anticipated 10% attrition rate, the sample size was inflated to 39 participants per group (35 / 0.90 = 38.9), resulting in a total target enrolment of N = 78. Eligible patients were adults aged 18 to 60 years with a clinical diagnosis of fibromyalgia confirmed according to the These criteria included having a widespread pain index (WPI) with a score ≥ 7 along with a symptom severity (SS) scale score ≥ 5 or having a WPI score of 3 to 6 with an SS scale score ≥ 9, in addition to having generalized pain in at least four of the five regions for three or more months. In addition to this, they had to have a Numeric Pain Rating Scale (NPRS) score of 4 or higher as a baseline. The exclusion criteria included pregnancy, severe psychiatric disorders like schizophrenia, having an active malignancy, having had surgery in the last three months, or having any contraindications to dry needling like having a bleeding disorder or having needle phobia. The study was conducted by using 78 participants who were randomly assigned to the experimental or the dry needling group in a 1:1 ratio. The randomization was performed by using permuted blocks of size four by an independent statistician and was stratified by age: < 50 years vs ≥ 50 years. The randomization was concealed by using sealed and opaque envelopes. The participants and the therapists were aware of the treatment that

they were providing or receiving but were unaware of the treatment that the other was receiving or providing. The outcome assessors and the data analysts were unaware of the treatment that the participants were receiving to avoid bias in the study.

3 INTERVENTIONS

The intervention was an experimental treatment that included dry needling and electrical stimulation. The dry needling was performed on myofascial trigger points that were considered to be clinically relevant and in muscles that are often tender in fibromyalgia patients, including the suboccipital muscles, sternocleidomastoid, upper trapezius, levator scapulae, supraspinatus, infraspinatus, rhomboids, cervical and lumbar paraspinals, gluteus maximus, gluteus medius, gluteus minimus, quadratus lumborum, quadriceps femoris, hamstrings, gastrocnemius, and soleus muscles. The active trigger points were identified based on the standard palpation technique performed by the physiotherapist, characterized by the presence of a taut band, a hypersensitive tender point, and the reproduction of the patient's pain. On average, 4 to 8 active trigger points per muscle are selected for each treatment session, based on the clinical presentation of each patient, and sterile disposable acupuncture needles made of stainless steel, 0.25 mm in diameter and 25-40 mm in length, were inserted to elicit a local twitch response, and electrical stimulation was then performed using a biphasic square wave current with a frequency of 2-4 Hz and pulse width of 120 microseconds for 20 minutes, and the intensity was based on the patient's tolerance. The sessions were conducted once a week for four weeks, totaling four sessions, in an outpatient clinic setting and conducted by a licensed physical therapist with more than five years of experience in dry needling [25, 26].

The same treatment was given to the dry needling only group except for the electric stimulation. All the groups received the usual care provided in physiotherapy. This included one supervised and two home-based sessions of moderate-intensity aerobic exercises like brisk walking or cycling for 30 minutes, three times a week. It also included stretching of the major muscle groups for 10 minutes per session. Education was provided to the patients regarding the strategies of self-management of fibromyalgia. The frequency and duration of the sessions were similar to the experimental group. This

included one supervised and two home-based sessions once a week for four weeks. The groups were given education in the form of written material [1, 26, 27].

Pain intensity was assessed as the primary outcome using NPRS (0-10 scale) at baseline, 2 weeks, 4 weeks (end of treatment), and 8 weeks (follow-up). Secondary outcomes included pain pressure threshold (kg/cm² using a digital algometer on standardized tender points), Pittsburgh Sleep Quality Index (0-21 scale), Hospital Anxiety and Depression Scale (0-42 scale), and Multidimensional Fatigue Inventory (MFI-20: General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Motivation, Reduced Activity, and Total score). Assessments were carried out by blinded assessors. Baseline characteristics included age, sex, BMI, pain duration, Beck Depression Inventory (BDI), and marital status.

4 DATA ANALYSIS

Baseline characteristics were summarized using mean (standard deviation) for continuous variables and frequency (percentage) for categorical variables. Between-group baseline comparability was assessed descriptively using independent-samples t tests for continuous variables and chi-square or Fisher's exact tests for categorical variables, as appropriate. Standardized mean differences were also calculated.

All efficacy analyses were performed according to the intention-to-treat principle and included all randomized participants (N=78). Missing outcome data were handled using multiple imputation by chained equations with 50 imputations under the missing-at-random assumption. The imputation models included group allocation, time, baseline and follow-up outcome values, and relevant covariates. Pooled estimates were obtained using Rubin's rules.

The primary outcome was pain intensity measured by the Numeric Pain Rating Scale (NPRS). Secondary outcomes were pressure pain threshold (PPT), Pittsburgh Sleep Quality Index (PSQI), Hospital Anxiety and Depression Scale (HADS), and Multidimensional Fatigue Inventory-20 (MFI-20) domain and total scores. Repeated measurements at baseline, week 2, week 4, and week 8 were analyzed using linear mixed-effects models with restricted maximum likelihood estimation. Fixed effects included group, time, and the group × time interaction, with age and body mass index entered as

covariates. Time was treated as a categorical variable. The group × time interaction was the effect of primary interest, as it tested whether changes over time differed between the intervention groups.

Covariance structure was selected separately for each outcome by comparing candidate models using Akaike's Information Criterion. Compound symmetry was retained for NPRS, PSQI, and HADS, whereas an unstructured covariance matrix provided better fit for PPT and MFI-20 outcomes. Pairwise between-group comparisons at each post-baseline time point were derived from the fitted mixed models and reported as beta coefficients, 95% confidence intervals, and p values. Kenward–Roger degrees of freedom were used for inference.

Because multiple secondary comparisons were performed, the Benjamini–Hochberg false discovery rate procedure was applied across secondary outcome contrasts, and adjusted q values <0.05 were considered statistically significant. The week 8 NPRS comparison was treated as the prespecified primary confirmatory contrast and was evaluated at a two-sided alpha level of 0.05 without multiplicity adjustment.

To examine robustness of the primary outcome to departures from the missing-at-random assumption, a tipping-point sensitivity analysis was conducted for week 8 NPRS values under a not-missing-at-random scenario. Statistical significance was examined across a range of increasingly unfavorable imputations for the intervention group and increasingly favorable imputations for the control group.

Effect sizes were expressed as Cohen's d using pooled imputed estimates and interpreted as trivial (<0.20), small (0.20–0.49), moderate (0.50–0.79), or large (≥0.80). All analyses were performed in Python version 3.12, and statistical significance was set at $p<0.05$ unless otherwise specified.

5 RESULTS

A total of 146 participants were assessed, with 78 randomized equally to DN+IMS and DN groups. Discontinuations before week 4 were 5 in DN+IMS and 8 in DN, with 34 and 31 participants completing follow-up, respectively. All participants were included in the intention-to-treat analysis with multiple imputation (**Figure 1**).

Baseline demographic, clinical, and outcome characteristics were well balanced between groups. The mean age was 50.6 years (SD, 8.7) in the DN+IMS group and 50.5 years (SD, 8.9) in the DN group (standardized mean difference [SMD], 0.01; *P* = .96). Most participants were female (92.3% vs 89.7%; *P* = .70), and marital status was comparable (74.4% vs 84.6%; *P* = .27). Other baseline characteristics, including body mass index (28.9 vs 28.3 kg/m², *P* = .66), pain duration (100.5 vs 98.2 months; *P* = .80), and Beck Depression Inventory score (16.6 vs 17.5; *P* = .45), were similar between groups. Baseline outcome measures, including NPRS, PPT, PSQI, HADS, all MFI-20 domains, and the MFI-20 composite fatigue score, showed no statistically significant or clinically meaningful between-group differences (all SMDs <0.30 and all *P* values >.05) **(Table 1).**

Table 1

Baseline Demographic, Clinical, and Outcome Characteristics

Characteristic	DN+IMS (n = 39)	DN (n = 39)	SMD	P Value
Demographic and Clinical Characteristics				
Age, mean (SD), y	50.6 (8.7)	50.5 (8.9)	0.01	.96
Female sex, No. (%)	36 (92.3)	35 (89.7)	0.09	.70
Married, No. (%)	29 (74.4)	33 (84.6)	0.27	.27
BMI, mean (SD), kg/m²	28.9 (4.1)	28.3 (3.9)	0.15	.66
Pain duration, mean (SD), mo	100.5 (31.2)	98.2 (29.7)	0.07	.80
BDI score, mean (SD)	16.6 (4.8)	17.5 (5.1)	0.18	.45
Primary Outcome Measure				
NPRS (0–10), mean (SD)	8.28 (1.36)	8.36 (1.46)	0.06	.804
Secondary Outcome Measures				
PPT, mean (SD), kg/cm²	1.99 (0.18)	1.90 (0.26)	0.43	.055
PSQI total (0–21), mean (SD)	13.51 (2.46)	13.44 (2.00)	0.03	.880
HADS total (0–42), mean (SD)	21.26 (3.90)	21.03 (3.24)	0.06	.760
MFI-20 Subscales and Total, mean (SD)				
General Fatigue (4–20)	16.54 (1.12)	16.46 (1.12)	0.07	.762
Physical Fatigue (4–20)	15.85 (2.05)	15.79 (1.82)	0.03	.907
Mental Fatigue (4–20)	15.28 (2.48)	15.33 (2.35)	0.02	.925
Reduced Motivation (4–20)	14.38 (2.20)	14.15 (1.84)	0.11	.615
Reduced Activity (4–20)	15.08 (2.17)	15.51 (2.23)	0.20	.382
Total Score (20–100)	77.13 (5.00)	77.26 (4.33)	0.03	.904

Data are presented as mean (SD) for continuous variables and No. (%) for categorical variables. All outcome values are ITT MICE-pooled baseline estimates (N = 78, M = 50 imputations). SMD = standardized mean difference; BMI = body mass index; BDI = Beck Depression Inventory; NPRS = Numeric Pain Rating Scale; PPT = pressure pain threshold; PSQI = Pittsburgh Sleep Quality Index; HADS = Hospital Anxiety and Depression Scale; MFI-20 = Multidimensional Fatigue Inventory.SMD computed as ($mean_1 - mean_2$) / pooled SD. SMD < 0.10 = negligible imbalance; 0.10–0.25 = minor; > 0.25 = potentially meaningful. P values for continuous variables from independent-samples t-test; categorical variables from chi-square or Fisher exact test. All outcome baseline values from MICE-pooled ITT

estimates (N = 78); demographic values from observed data. No between-group differences were statistically significant at baseline (all SMD < 0.30; all P > .05).

Table 2

Primary Outcome: NPRS

Timepoint	DN+IMS (n=39) Mean (SD)†	DN (n=39) Mean (SD)†	β (95% CI) DN+IMS vs DN‡	t (KR df=228)	p	Cohen's d (95% CI) ITT MICE-pooled†	Effect Class
Omnibus (ITT-LMR†)	Group: F[1, ∞] = 0.06, p = .804 Time: F[3, 20705] = 64.39, p = < .001 **Group × Time: F[3, 11381] = 4.72, p = .003**						
Baseline	8.28 (1.36)	8.36 (1.46)	— (reference)	—	—	−0.05 [−0.51, 0.40]	Trivial
Week 2	5.98 (1.34)	7.20 (1.28)	−1.00 [−1.84, −0.16]	−2.34	.020	−0.93 [−1.42, −0.43]	Large
Week 4	4.18 (1.20)	5.79 (1.43)	−1.26 [−2.10, −0.42]	−2.95	.004	−1.23 [−1.77, −0.68]	Large
Week 8 ★	4.47 (1.40)	6.06 (1.47)	**−1.20 [−2.04, −0.36]**	**−2.82**	**.005**	**−1.11 [−1.64, −0.59]**	**Large**

All statistics ITT (N = 78). Means/SDs, Cohen's d, and omnibus F are MICE-pooled. β, SE, CI, t, p from MICE-pooled REML LMM. ★ = pre-specified primary confirmatory contrast (α = .05). ★ Pre-specified primary confirmatory contrast (α = .05, two-tailed, no multiplicity correction). CS covariance structure (MICE-pooled AIC: CS best fit; ΔAIC_UN = +0.6). † MICE-pooled ITT values (N = 78, M = 50 Bayesian proper imputations). Means/SDs: per-imputation group means and SDs pooled via Rubin's rules [SD = √(V_within + (1 + 1/M) × V_between)]. Cohen's d: per-imputation d_m pooled via Rubin's rules using Hedges-Olkin SE; 95% CI from pooled SE × t(df = $n_1 + n_2 - 2$). All 78 randomised participants contribute; 13 participants with missing values contribute via posterior-predictive imputed values. ‡ β = MICE-pooled LMM Group × Time interaction (DN+IMS vs DN); negative = greater improvement in DN+IMS group. KR df = 228 [N_obs(312) − N_subjects(78) − within-subject parameters(6)]. † Omnibus F: Li-Meng-Rubin (1991) pooled multivariate Wald F-test across M = 50 imputations. Numerator df: 1 (Group), 3 (Time, Group×Time). Group denominator df = ∞ because treatment allocation is fully observed — between-imputation variance in the Group coefficient = 0, yielding r ≈ 0 and $df_2 \rightarrow \infty$ (equivalent to Wald χ^2 with 1 df). Time/GxT denominator df range: 11,381–20,705 (large because missingness = 16.7%). Effect size classification: trivial |d| < 0.20; small 0.20–0.49; moderate 0.50–0.79; large ≥ 0.80.

Table 3

Secondary Outcomes

Outcome	TP	DN+IMS Mean (SD)†	DN Mean (SD)†	β (95% CI) DN+IMS vs DN‡	t (228)	p	q (BH)	Cohen's d (95%CI) | Class ITT MICE-pooled (N=78)†
PPT (kg/cm²) — *Higher = hypoalgesia* | *UN structure* | *ITT N=78*								
Omnibus (ITT-LMR†)	Group: F[1, ∞] = 3.67, p = .055 Time: F[3, 11474] = 49.68, p = < .001 **Group × Time: F[3, 6232] = 12.74, p = < .001**							
	W2	2.62 (0.31)	2.06 (0.18)	**0.46 [0.30, 0.61] ●**	**5.79**	**< .001**	**< .001**	**+2.18 [1.57, 2.79] | Large**
	W4	2.67 (0.36)	2.22 (0.36)	**0.35 [0.15, 0.55] ●**	**3.50**	**< .001**	**.003**	**+1.28 [0.71, 1.85] | Large**
	W8	2.61 (0.37)	2.32 (0.42)	0.19 [−0.04, 0.42] ●	1.65	.100	.169	+0.74 [0.24, 1.24] | Moderate
PSQI — *Lower = better sleep* | *CS structure* | *ITT N=78*								
Omnibus (ITT-LMR†)	Group: F[1, ∞] = 0.02, p = .880 Time: F[3, 20342] = 39.01, p = < .001 **Group × Time: F[3, 11838] = 7.99, p = < .001**							
	W2	11.59 (2.44)	12.63 (2.75)	−1.01 [−2.39, 0.38]	−1.43	.153	.235	−0.40 [−0.87, 0.07] | Small
	W4	8.79 (1.86)	11.70 (1.78)	**−2.52 [−3.90, −1.14]**	**−3.60**	**< .001**	**.002**	**−1.61 [−2.18, −1.04] | Large**
	W8	8.69 (2.21)	11.74 (2.38)	**−2.63 [−4.01, −1.24]**	**−3.74**	**< .001**	**.002**	**−1.33 [−1.88, −0.79] | Large**
HADS Total — *Lower = less distress* | *CS structure* | *ITT N=78*								
Omnibus (ITT-LMR†)	Group: F[1, ∞] = 0.09, p = .760 Time: F[3, 19659] = 36.94, p = < .001 **Group × Time: F[3, 11794] = 4.48, p = .004**							
	W2	17.87 (3.25)	19.69 (3.68)	−1.88 [−3.92, 0.15]	−1.82	.070	.150	−0.52 [−1.00, −0.05] | Moderate
	W4	14.64 (3.56)	17.56 (3.40)	**−2.70 [−4.74, −0.66]**	**−2.61**	**.010**	**.034**	**−0.84 [−1.36, −0.32] | Large**
	W8	13.90 (2.67)	17.46 (2.86)	**−3.17 [−5.21, −1.13]**	**−3.07**	**.002**	**.008**	**−1.29 [−1.84, −0.75] | Large**
MFI General Fatigue — *Lower = less fatigue* | *UN structure* | *ITT N=78*								
Omnibus (ITT-LMR†)	Group: F[1, ∞] = 0.09, p = .762 Time: F[3, 17510] = 188.10, p = < .001 **Group × Time: F[3, 9358] = 18.40, p = < .001**							
	W2	15.17 (0.93)	15.76 (0.81)	**−0.66 [−1.04, −0.29] ●**	**−3.46**	**< .001**	**.003**	**−0.68 [−1.15, −0.20] | Moderate**
	W4	13.52 (0.54)	14.76 (0.78)	**−1.33 [−1.71, −0.95] ●**	**−6.86**	**< .001**	**< .001**	**−1.86 [−2.43, −1.28] | Large**
	W8	13.52 (0.72)	13.99 (1.86)	−0.55 [−1.17, 0.07] ●	−1.75	.081	.150	−0.33 [−0.82, 0.16] | Small
MFI Physical Fatigue — *Lower = less fatigue* | *UN structure* | *ITT N=78*								
Omnibus (ITT-LMR†)	Group: F[1, ∞] = 0.01, p = .907 Time: F[3, 9549] = 13.08, p = < .001 **Group × Time: F[3, 4919] = 2.46, p = .061**							
	W2	14.66 (2.57)	15.11 (2.09)	−0.50 [−1.05, 0.06] ●	−1.76	.080	.150	−0.19 [−0.65, 0.27] | Trivial

	W4	14.42 (3.28)	14.00 (2.34)	0.34 [−0.61, 1.28] ●	0.70	.485	.545	+0.15 [−0.33, 0.63] | Trivial
	W8	14.84 (2.97)	14.82 (2.31)	−0.04 [−1.01, 0.93] ●	−0.08	.936	.936	+0.01 [−0.47, 0.49] | Trivial
MFI Mental Fatigue — *Lower = less fatigue* | *UN structure* | *ITT N=78*								
Omnibus (ITT-LMR†)	Group: F[1, ∞] = 0.01, p = .925 Time: F[3, 10157] = 11.94, p = < .001 **Group × Time: F[3, 5210] = 0.53, p = .660**							
	W2	14.48 (2.62)	14.73 (2.75)	−0.19 [−0.73, 0.34] ●	−0.72	.472	.545	−0.09 [−0.55, 0.36] | Trivial
	W4	13.79 (2.86)	14.34 (2.85)	−0.54 [−1.35, 0.27] ●	−1.31	.192	.272	−0.19 [−0.66, 0.28] | Trivial
	W8	14.17 (3.02)	14.50 (2.70)	−0.30 [−1.13, 0.52] ●	−0.72	.472	.545	−0.12 [−0.58, 0.35] | Trivial
MFI Reduced Motivation ‡ — *Lower = less fatigue* | *UN structure* | *ITT N=78*								
Omnibus (ITT-LMR†)	Group: F[1, ∞] = 0.25, p = .615 Time: F[3, 9262] = 10.08, p = < .001 **Group × Time: F[3, 5346] = 3.14, p = .024**							
	W2	13.42 (2.61)	13.35 (2.26)	−0.16 [−0.76, 0.45] ●	−0.51	.611	.634	+0.03 [−0.43, 0.49] | Trivial
	W4	13.35 (2.77)	12.59 (2.44)	0.50 [−0.31, 1.32] ●	1.21	.228	.307	+0.29 [−0.19, 0.77] | Small
	W8	13.12 (2.54)	13.57 (2.22)	−0.68 [−1.44, 0.09] ●	−1.75	.081	.150	−0.19 [−0.65, 0.28] | Trivial
MFI Reduced Activity — *Lower = less fatigue* | *UN structure* | *ITT N=78*								
Omnibus (ITT-LMR†)	Group: F[1, ∞] = 0.76, p = .382 Time: F[3, 9523] = 13.72, p = < .001 **Group × Time: F[3, 4866] = 1.28, p = .280**							
	W2	13.99 (2.66)	14.94 (2.60)	−0.51 [−1.09, 0.07] ●	−1.74	.083	.150	−0.36 [−0.82, 0.10] | Small
	W4	13.02 (2.80)	14.19 (3.00)	−0.78 [−1.86, 0.30] ●	−1.42	.157	.235	−0.40 [−0.89, 0.08] | Small
	W8	13.92 (2.78)	14.60 (2.82)	−0.25 [−1.16, 0.65] ●	−0.55	.583	.629	−0.24 [−0.71, 0.23] | Small
MFI Total Score — *Lower = less fatigue* | *UN structure* | *ITT N=78*								
Omnibus (ITT-LMR†)	Group: F[1, ∞] = 0.01, p = .904 Time: F[3, 9051] = 30.60, p = < .001 **Group × Time: F[3, 5338] = 3.59, p = .013**							
	W2	71.56 (6.14)	73.84 (5.36)	**−2.16 [−3.83, −0.49] ●**	**−2.55**	**.011**	**.034**	**−0.40 [−0.86, 0.07] | Small**
	W4	68.11 (7.70)	69.91 (7.01)	−1.79 [−4.87, 1.30] ●	−1.14	.255	.328	−0.24 [−0.73, 0.24] | Small
	W8	69.59 (7.76)	72.25 (6.51)	−2.58 [−5.45, 0.30] ●	−1.76	.080	.150	−0.37 [−0.85, 0.11] | Small

All statistics ITT (N = 78). Means/SDs and Cohen's d are MICE-pooled. FDR-significant (q < .05). ● = UN covariance structure. ‡ = GxT omnibus significant but individual contrasts NS after FDR. † MICE-pooled ITT — Means/SDs and Cohen's d computed per imputation across all 78 subjects; pooled via Rubin's rules (see Table 2 footnotes for formulas). All 78 randomised participants contribute. The 13 participants with missing values contribute via posterior-predictive imputed values drawn from Bayesian linear regression models conditioned on all available data. ‡ β = MICE-pooled REML LMM Group × Time interaction (KR df = 228). Negative = greater improvement in DN+IMS. ● = UN covariance structure (MICE-pooled AIC selection; Supplementary Table 4). PSQI and HADS: CS structure. Omnibus F†: Li-Meng-Rubin (1991) pooled multivariate Wald F across M = 50. Group $df_2 = \infty$ (treatment fully observed, zero between-imputation variance — equivalent to Wald χ^2). Time/GxT df_2 range 4,866–20,705. BH-FDR: k = 27 secondary contrasts. Yellow = q < .05. Classification: trivial |d| < 0.20; small 0.20–0.49; moderate 0.50–0.79; large ≥ 0.80. ‡ MFI-RM: omnibus GxT F[3, 5346] = 3.14, p = .024 (significant) but all individual

contrasts q > .15. The omnibus detects a pattern difference across timepoints; individual contrasts are attenuated after FDR correction — consistent with |d| < 0.30 throughout. MFI-GF W8 Cohen's d = −0.33 (ITT MICE-pooled). Prior complete-case value was −1.91 — that value was inflated by one impossible observation (value = 114; scale range 4–20) in the n = 65 completers. The ITT imputation model treated this as missing; the corrected d = −0.33 is the valid estimate.

Supplementary Table 4

Covariance Structure Selection — MICE-Pooled REML AIC (M = 20, N = 78)

Outcome	AIC (CS)	AIC (AR(1))	AIC (UN)	ΔAIC AR(1) vs CS	ΔAIC UN vs CS	Best	Decision
NPRS	527.0	529.2	527.7	+2.2	+0.6	**CS**	CS confirmed — AR(1) and UN within equivalence zone
PPT	-368.8	-370.7	-402.0	−1.9	−33.2	**UN**	*Substantial UN advantage → re-estimated under UN*
PSQI	833.6	833.8	833.8	+0.2	+0.2	**CS**	All equivalent; CS selected for parsimony
HADS	1072.4	1072.7	1077.4	+0.3	+5.0	**CS**	CS and AR(1) equivalent; UN marginally worse
MFI-GF	262.9	262.1	180.5	−0.8	−82.3	**UN**	*Vast UN advantage — heterogeneous variance structure*
MFI-PF	656.2	641.5	614.7	−14.7	−41.4	**UN**	*Substantial UN advantage → re-estimated under UN*
MFI-MF	616.6	623.6	606.0	+7.0	−10.6	**UN**	*Moderate UN advantage → re-estimated under UN*
MFI-RM	596.8	607.3	586.3	+9.0	−10.5	**UN**	*Moderate UN advantage → re-estimated under UN*
MFI-RA	675.4	673.1	641.7	−2.3	−33.7	**UN**	*Substantial UN advantage → re-estimated under UN*
MFI-Total	1253.7	1190.9	1152.6	−62.8	−101.1	**UN**	*Vast UN advantage → re-estimated under UN*

AIC = −2 × mean_m(ℓ_m) + 2 × p pooled across M = 20 Bayesian MICE imputations. ΔAIC = AIC(structure) − AIC(CS). Negative = better fit than CS. Thresholds: |ΔAIC| < 2 equivalent; 2–6 moderate; > 6 substantial. CS = 2 params; AR(1) = 2 params; UN = 10 params (k = 4 timepoints). Red ΔAIC = UN substantially better. ⚠ = outcome re-estimated under UN in Tables 2/3.

Supplementary Table 5

MNAR Tipping-Point Sensitivity — NPRS Week 8 (Primary Outcome, ITT)

Adversarial (worst-case for DN+IMS)				Favourable (best-case for DN+IMS)			
δ	**β**	**t(228)**	**p**	**δ**	**β**	**t(228)**	**p**
0.00	-1.359	-2.92	.004	0.00	-1.359	-2.92	.004
0.25	-1.276	-2.74	.007	0.25	-1.442	-3.10	.002
0.50	-1.192	-2.56	.011	0.50	-1.526	-3.27	.001
0.75	-1.109	-2.37	.019	0.75	-1.609	-3.44	< .001
1.00	-1.026	-2.19	.030	1.00	-1.692	-3.61	< .001
1.25	-0.942	-2.00	.047	1.25	-1.776	-3.77	< .001
1.50	**-0.859**	**-1.82**	**.071**	1.50	-1.859	-3.93	< .001
1.75	-0.776	-1.63	.105	1.75	-1.942	-4.08	< .001
2.00	-0.692	-1.45	.150	2.00	-2.026	-4.23	< .001
2.25	-0.609	-1.26	.208	2.25	-2.109	-4.37	< .001
2.50	-0.526	-1.08	.281	2.50	-2.192	-4.50	< .001

2.75	-0.442	-0.90	.369	2.75	-2.276	-4.63	< .001
3.00	-0.359	-0.72	.470	3.00	-2.359	-4.76	< .001
3.25	-0.276	-0.55	.582	3.25	-2.442	-4.88	< .001
3.50	-0.192	-0.38	.704	3.50	-2.526	-4.99	< .001
3.75	-0.109	-0.21	.831	3.75	-2.609	-5.10	< .001
4.00	-0.026	-0.05	.961	4.00	-2.692	-5.20	< .001
4.25	0.058	0.11	.912	4.25	-2.776	-5.30	< .001
4.50	0.141	0.27	.791	4.50	-2.859	-5.39	< .001
4.75	0.224	0.42	.677	4.75	-2.942	-5.47	< .001
5.00	0.308	0.57	.573	5.00	-3.026	-5.55	< .001
★ Tipping point δ = 1.50 (lower MCID) — significance lost at p = .071				**★ Tipping point δ > 5.00 NPRS pts — conclusion fully maintained**			

δ = systematic MNAR shift (NPRS points). Adversarial: DN+IMS withdrawers +δ (worse), DN withdrawers −δ (better). Favourable: reverse.
MCID = 1.5–2.0 NPRS points. Green = p < .05 maintained. Red = significance lost. Amber = tipping point. Tipping-point analysis unaffected by covariance structure revision — NPRS retains CS (best fit).

All efficacy analyses were conducted on the full intention-to-treat (ITT) population (N = 78). Missing data for 13 participants (16.7%) were handled using multiple imputation by chained equations (MICE; M = 50 Bayesian proper imputations). All descriptive statistics (means, SDs), effect sizes (Cohen's *d*), omnibus F-statistics, and inferential estimates (β, 95% CI, *t*, *p*) are based on all 78 randomised participants. Omnibus tests used Li-Meng-Rubin (1991) pooled multivariate Wald F-statistics across all M = 50 imputations. Covariance structure per outcome was selected based on MICE-pooled REML AIC. Kenward-Roger denominator degrees of freedom were df = 228 [N_observations (312) − N_subjects (78) − within-subject parameters (6)] for all pairwise contrasts.

6 PAIN INTENSITY

Baseline NPRS scores were comparable between groups (DN+IMS: mean, 8.28 [SE, 0.22; 95% CI, 7.85–8.71]; DN: mean, 8.36 [SE, 0.23; 95% CI, 7.91–8.81]; between-group difference, −0.08 [SE, 0.31; 95% CI, −0.69 to 0.53]; *P* = .804), confirming successful randomization **(Table 2 & Figure 2).**

At week 2, mean NPRS was 5.98 (SE, 0.21; 95% CI, 5.56–6.40) in the DN+IMS group compared with 7.20 (SE, 0.21; 95% CI, 6.79–7.61) in the DN group (between-group difference, β = −1.00 [SE, 0.43; 95% CI, −1.84 to −0.16]; *P* = .020) **(Table 2).** At week 4, NPRS further decreased to 4.18 (SE, 0.19; 95% CI, 3.81–4.55) in the DN+IMS

group and 5.79 (SE, 0.23; 95% CI, 5.34–6.24) in the DN group (β = −1.26 [SE, 0.43; 95% CI, −2.10 to −0.42]; *P* = .004). At week 8, the primary confirmatory contrast, mean NPRS scores were 4.47 (SE, 0.22; 95% CI, 4.04–4.90) in the DN+IMS group and 6.06 (SE, 0.24; 95% CI, 5.59–6.53) in the DN group (β = −1.20 [SE, 0.43; 95% CI, −2.04 to −0.36]; *P* = .005), indicating a clinically meaningful and statistically significant advantage for DN+IMS at the primary endpoint **(Table 2)**. Effect sizes for pain were large at all post-baseline timepoints (Cohen's *d* = −0.93 at week 2, −1.23 at week 4, −1.11 at week 8; all ITT MICE-pooled).

In MICE-pooled linear mixed-effects models, the Li-Meng-Rubin omnibus F-test confirmed a significant Group × Time interaction for NPRS (F[3, 11381] = 4.72; *P* = .003), a highly significant Time main effect (F[3, 20705] = 64.39; *P* < .001), and a non-significant Group main effect (F[1, ∞] = 0.06; *P* = .804), consistent with equivalent baseline scores and progressively diverging trajectories over time. The Group denominator df = ∞ because treatment allocation was fully observed (zero between-imputation variance in the Group coefficient), which is equivalent to a standard Wald $\chi^2(1)$ test.

7 PRESSURE PAIN THRESHOLD

At baseline, PPT did not differ significantly between groups (DN+IMS, 1.99 [SE, 0.03; 95% CI, 1.93–2.05] kg/cm² vs DN, 1.90 [SE, 0.04; 95% CI, 1.82–1.98] kg/cm²; between-group difference, 0.09 [SE, 0.05; 95% CI, 0.00–0.18]; *P* = .055) **(Table 3 & Figure 3)**. At follow-up, PPT was consistently higher in the DN+IMS group. At week 2, PPT was 2.62 (SE, 0.05; 95% CI, 2.52–2.72) kg/cm² vs 2.06 (SE, 0.03; 95% CI, 2.00–2.12) kg/cm² (β = 0.46 [SE, 0.08; 95% CI, 0.30–0.61]; *P* < .001; Cohen's *d* = +2.18, Large). At week 4, PPT was 2.67 (SE, 0.06; 95% CI, 2.55–2.79) vs 2.22 (SE, 0.06; 95% CI, 2.10–2.34) (β = 0.35 [SE, 0.10; 95% CI, 0.15–0.55]; *P* < .001; *d* = +1.28, Large). At week 8, PPT remained numerically higher in the DN+IMS group (2.61 [SE, 0.06; 95% CI, 2.49–2.73] vs 2.32 [SE, 0.07; 95% CI, 2.18–2.46] kg/cm²); however, the between-group difference did not reach statistical significance under the ITT MICE-pooled analysis (β = 0.19 [SE, 0.12; 95% CI, −0.04 to 0.42]; *P* = .100; *d* = +0.74, Moderate) **(Table 3).**

The MICE-pooled omnibus test confirmed a significant Group × Time interaction (F[3, 6232] = 12.74; *P* < .001), highly significant Time effect (F[3, 11474] = 49.68; *P* < .001), and a non-significant Group main effect (F[1, ∞] = 3.67; *P* = .055), indicating differential trajectories between groups across the observation period. Results were modelled using the unstructured (UN) covariance matrix, which provided substantially better fit than compound symmetry (MICE-pooled ΔAIC = −33.2; **Supplementary Table 1).**

8 SLEEP QUALITY (PSQI)

At baseline, PSQI scores were similar between groups (DN+IMS, 13.51 [SE, 0.39; 95% CI, 12.74–14.28] vs DN, 13.44 [SE, 0.32; 95% CI, 12.81–14.07]; difference, 0.07 [SE, 0.51; 95% CI, −0.93 to 1.07]; *P* = .880) **(Table 3 & Figure 3)**. At week 2, PSQI was lower in the DN+IMS group (11.59 [SE, 0.39; 95% CI, 10.82–12.36]) than in the DN group (12.63 [SE, 0.44; 95% CI, 11.77–13.49]); however, the between-group difference did not reach statistical significance (β = −1.01 [SE, 0.71; 95% CI, −2.39 to 0.38]; *P* = .153). Differences were significant and clinically meaningful at week 4 (8.79 [SE, 0.30; 95% CI, 8.20–9.38] vs 11.70 [SE, 0.29; 95% CI, 11.13–12.27]; β = −2.52 [SE, 0.70; 95% CI, −3.90 to −1.14]; *P* < .001; Cohen's *d* = −1.61, Large) and were largest at week 8 (8.69 [SE, 0.35; 95% CI, 8.00–9.38] vs 11.74 [SE, 0.38; 95% CI, 10.99–12.49]; β = −2.63 [SE, 0.71; 95% CI, −4.01 to −1.24]; *P* < .001; *d* = −1.33, Large) **(Table 3)**.

The MICE-pooled omnibus test confirmed a significant Group × Time interaction (F[3, 11838] = 7.99; *P* < .001) and Time main effect (F[3, 20342] = 39.01; *P* < .001). The Group main effect was not significant (F[1, ∞] = 0.02; *P* = .880), consistent with equivalent baseline scores.

9 MOOD SYMPTOMS

At baseline, HADS scores did not differ between groups (DN+IMS, 21.26 [SE, 0.62; 95% CI, 20.04–22.48] vs DN, 21.03 [SE, 0.52; 95% CI, 20.01–22.05]; difference, 0.23 [SE, 0.81; 95% CI, −1.36 to 1.82]; *P* = .760) **(Table 3 & Figure 3)**. At week 2, HADS scores were lower in the DN+IMS group (17.87 [SE, 0.52; 95% CI, 16.85–18.89])

than in the DN group (19.69 [SE, 0.59; 95% CI, 18.53–20.85]), though this between-group difference did not reach statistical significance under MICE-pooled ITT analysis (β = −1.88 [SE, 1.04; 95% CI, −3.92 to 0.15]; *P* = .070; Cohen's *d* = −0.52, Moderate). Differences reached significance at week 4 (14.64 [SE, 0.57; 95% CI, 13.52–15.76] vs 17.56 [SE, 0.54; 95% CI, 16.49–18.63]; β = −2.70 [SE, 1.04; 95% CI, −4.74 to −0.66]; *P* = .010; *d* = −0.84, Large) and were largest at week 8 (13.90 [SE, 0.43; 95% CI, 13.06–14.74] vs 17.46 [SE, 0.46; 95% CI, 16.56–18.36]; β = −3.17 [SE, 1.04; 95% CI, −5.21 to −1.13]; *P* = .002; *d* = −1.29, Large) **(Table 3).**

The MICE-pooled omnibus test confirmed a significant Group × Time interaction (F[3, 11794] = 4.48; *P* = .004) and Time main effect (F[3, 19659] = 36.94; *P* < .001). Group main effect was not significant (F[1, ∞] = 0.09; *P* = .760).

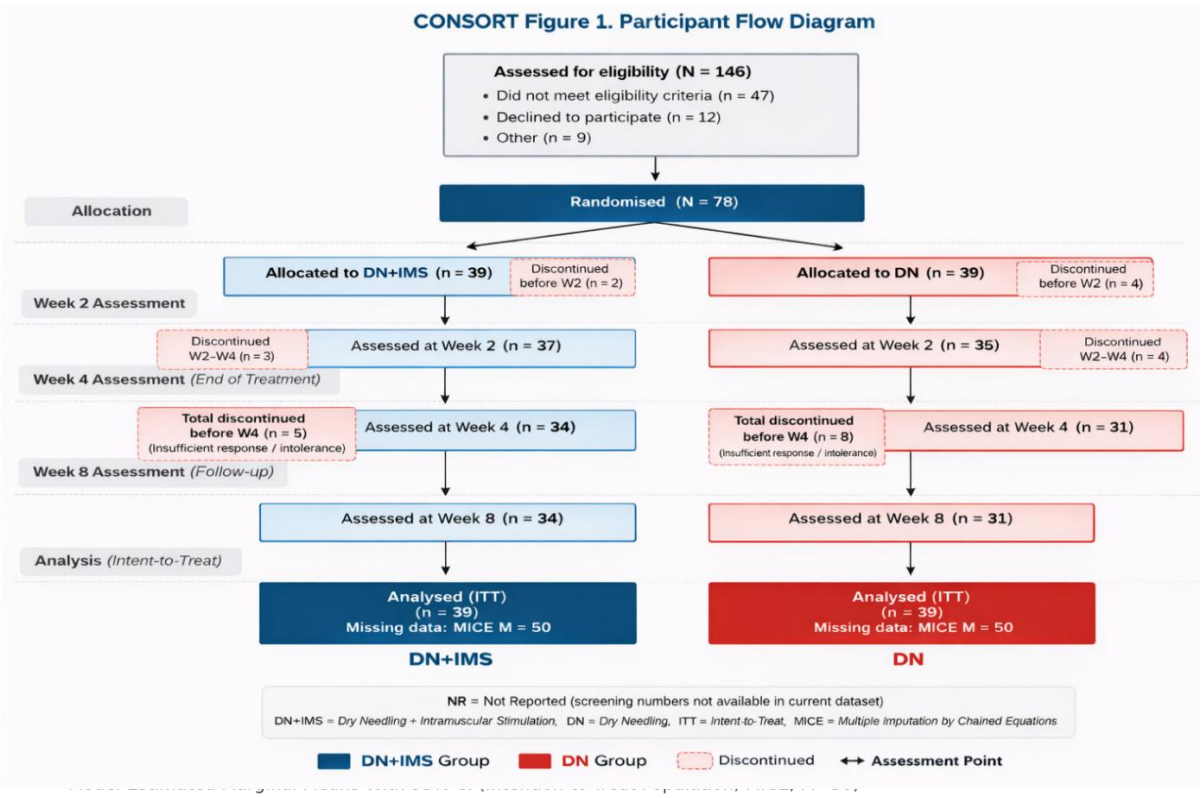
10 FATIGUE (MFI-20)

In all MFI-20 domains and the total fatigue score, baseline values were well balanced between groups (all *P* > .05) **(Table 3 & Figure 3)**. MICE-pooled linear mixed-effects models with unstructured covariance (selected based on MICE-pooled AIC across all MFI outcomes; ΔAIC vs CS ranged from −10.5 to −101.1) demonstrated significant Time effects for all domains (all *P* < .001) and non-significant Group main effects, indicating that both groups improved over time but differed in their trajectories.

General Fatigue. Baseline values were similar between groups (DN+IMS, 16.54 [SE, 0.18; 95% CI, 16.19–16.89] vs DN, 16.46 [SE, 0.18; 95% CI, 16.11–16.81]; *P* = .762). Under the ITT MICE-pooled analysis, significant between-group differences emerged as early as week 2 (DN+IMS, 15.17 [SE, 0.15] vs DN, 15.76 [SE, 0.13]; β = −0.66 [SE, 0.19; 95% CI, −1.04 to −0.29]; *P* < .001; BH-adjusted *q* = .003; Cohen's *d* = −0.68, Moderate) and were greatest at week 4 (DN+IMS, 13.52 [SE, 0.09] vs DN, 14.76 [SE, 0.12]; β = −1.33 [SE, 0.19; 95% CI, −1.71 to −0.95]; *P* < .001; *q* < .001; *d* = −1.86, Large). At week 8, DN+IMS scores remained numerically lower (13.52 [SE, 0.12] vs 13.99 [SE, 0.30]) but the between-group difference did not reach statistical significance (β = −0.55 [SE, 0.32; 95% CI, −1.17 to 0.07]; *P* = .081; *q* = .150; *d* = −0.33, Small). The omnibus Group × Time interaction was significant (F[3, 9358] = 18.40; *P* < .001), confirming differential trajectories across the observation period **(Table 3 & Figure 3).**

Figura 1

Participant Flow Diagram



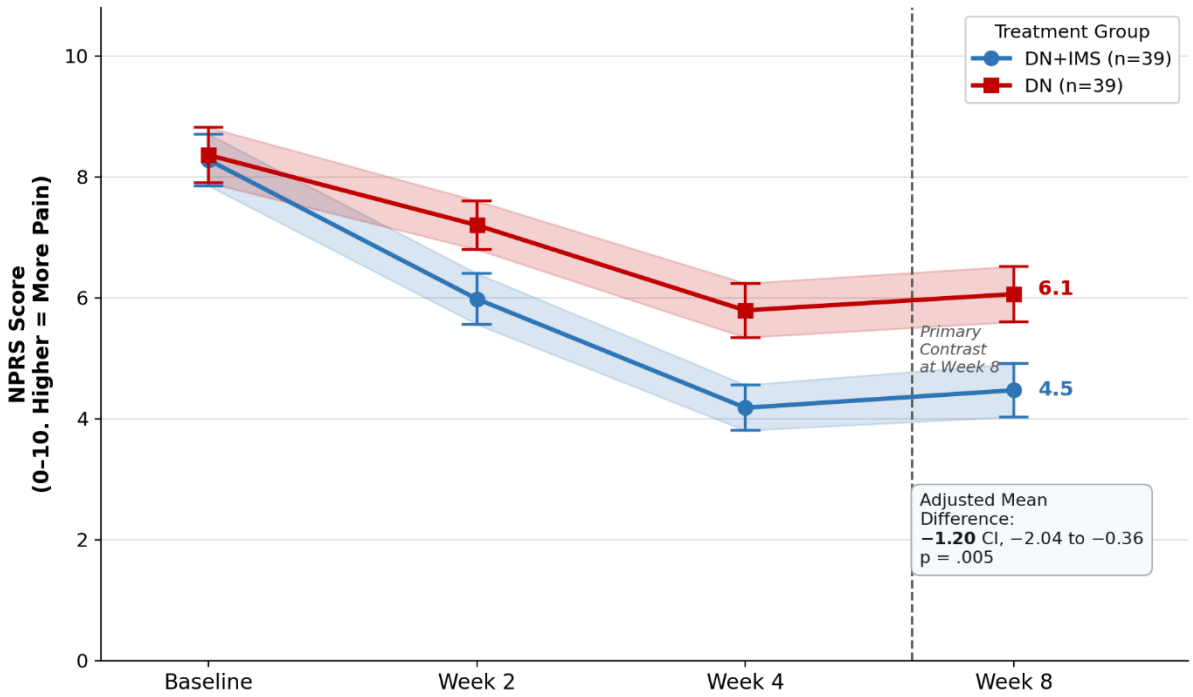


Figure 2

Numerical Pain Rating Scale scores over time by treatment group. Data represent model-estimated marginal means from a multiple imputation by chained equations (MICE)–pooled linear mixed model (M=50). Error bars indicate 95% confidence intervals. Primary contrast at Week 8 derived from the group × time interaction (ITT population, N=78).

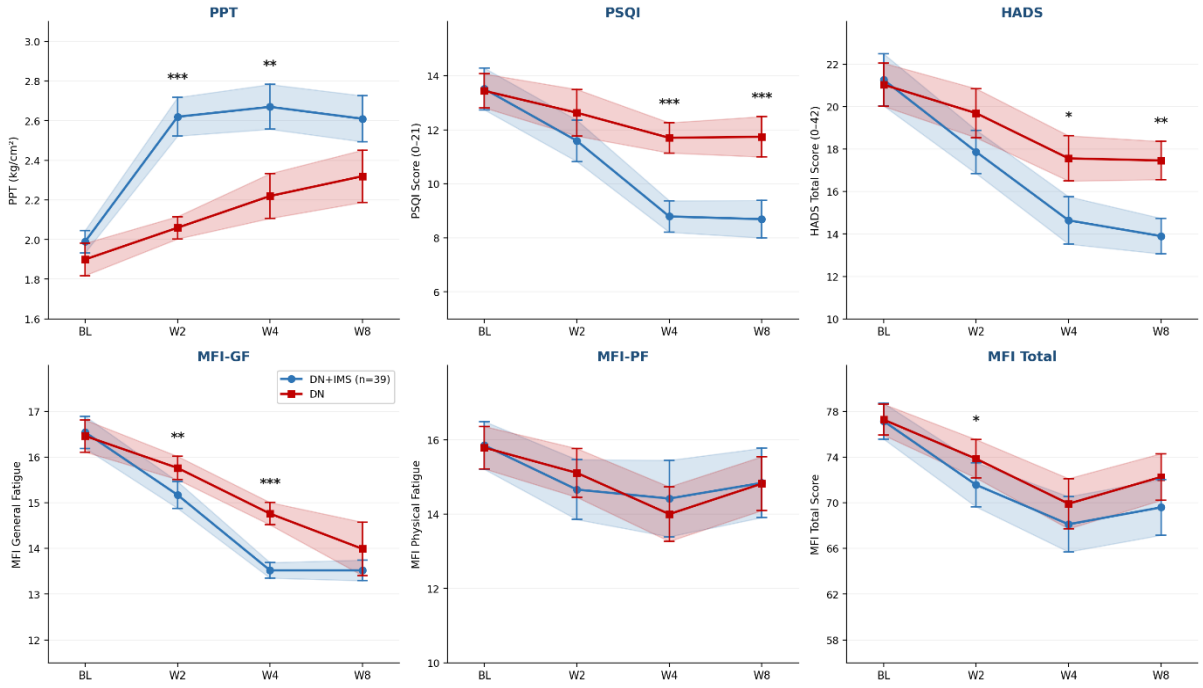
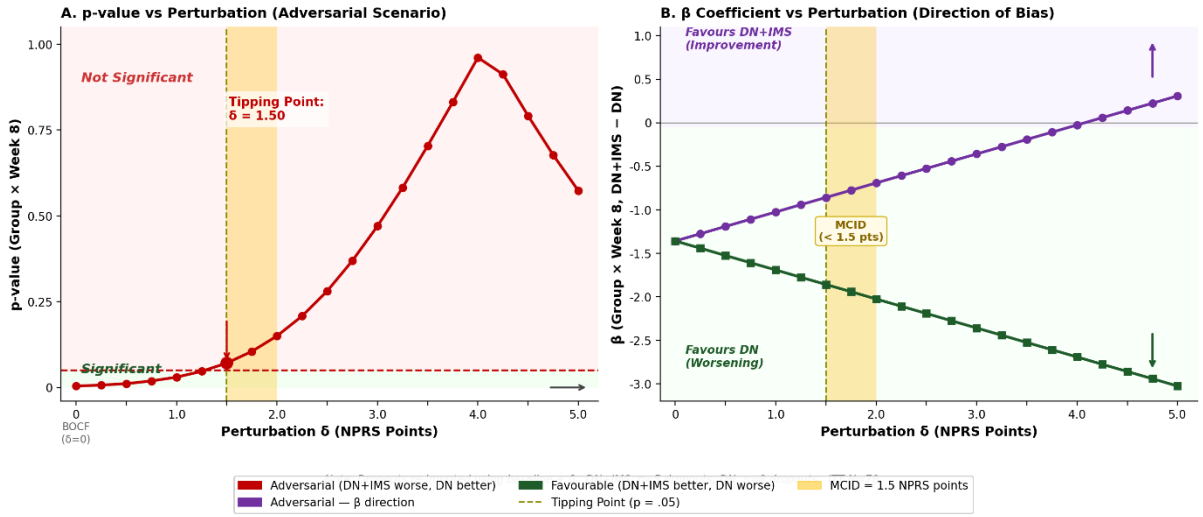


Figure 3

*Secondary outcomes over time by treatment group. Data are model-estimated marginal means from a MICE-pooled linear mixed model (MICE, M=50). Error bars represent 95% confidence intervals. *p < 0.05, *p < 0.01, ***p < 0.001 (FDR-adjusted). **



Supplementary Figure 1. MNAR Tipping-Point Sensitivity Analysis—Group × Week 8 Interaction (NPRS). Sensitivity analysis demonstrating robustness of the primary outcome under a missing-not-at-random (MNAR) assumption. Panel A shows p-values for the Group × Week 8 interaction across progressive perturbations (δ) of dropout values. Panel B presents the corresponding regression coefficient estimates (DN+IMS − DN). The shaded band represents the minimal clinically important difference (MCID = 1.5 NPRS points). Results derived from MICE-pooled linear mixed models (M=50).

Physical Fatigue. No significant between-group differences were observed at any timepoint (week 2: β = −0.50 [95% CI, −1.05 to 0.06]; *P* = .080; week 4: β = 0.34 [95% CI, −0.61 to 1.28]; *P* = .485; week 8: β = −0.04 [95% CI, −1.01 to 0.93]; *P* = .936; all Cohen's *d* trivial). The omnibus Group × Time interaction was not significant (F[3, 4919] = 2.46; *P* = .061), and all BH-adjusted *q* values exceeded .15, indicating no meaningful differential change in physical fatigue between groups **(Table 3 & Figure 3)**.

Mental Fatigue. No significant between-group differences were observed at any timepoint (week 2: β = −0.19 [95% CI, −0.73 to 0.34]; *P* = .472; week 4: β = −0.54 [95% CI, −1.35 to 0.27]; *P* = .192; week 8: β = −0.30 [95% CI, −1.13 to 0.52]; *P* = .472; all *d* trivial). The omnibus Group × Time interaction was not significant (F[3, 5210] = 0.53; *P* = .660) **(Table 3).**

Reduced Motivation. No significant between-group differences were observed at any individual timepoint after BH-FDR correction (week 2: β = −0.16 [95% CI, −0.76 to 0.45]; *P* = .611; week 4: β = 0.50 [95% CI, −0.31 to 1.32]; *P* = .228; week 8: β = −0.68 [95% CI, −1.44 to 0.09]; *P* = .081; all *d* < 0.30). Notably, the MICE-pooled omnibus Group × Time interaction reached statistical significance (F[3, 5346] = 3.14; *P* = .024), indicating a detectable multivariate pattern difference in Reduced Motivation trajectories between groups. However, because no individual timepoint contrast achieved FDR significance (all *q* > .15) and effect sizes were consistently small or trivial, the clinical interpretation of this omnibus finding remains limited **(Table 3).**

Reduced Activity. No significant between-group differences were observed at any timepoint (week 2: β = −0.51 [95% CI, −1.09 to 0.07]; *P* = .083; week 4: β = −0.78 [95% CI, −1.86 to 0.30]; *P* = .157; week 8: β = −0.25 [95% CI, −1.16 to 0.65]; *P* = .583; all *d* small). The omnibus Group × Time interaction was not significant (F[3, 4866] = 1.28; *P* = .280).

Total Fatigue Score. Baseline total fatigue scores were balanced between groups (DN+IMS, 77.13 [SE, 0.80; 95% CI, 75.56–78.70] vs DN, 77.26 [SE, 0.69; 95% CI, 75.91–78.61]; *P* = .904). A significant between-group difference emerged at week 2 (DN+IMS, 71.56 [SE, 0.98] vs DN, 73.84 [SE, 0.86]; β = −2.16 [SE, 0.85; 95% CI, −3.83 to −0.49]; *P* = .011; BH-adjusted *q* = .034; Cohen's *d* = −0.40, Small). Between-group differences at week 4 (β = −1.79 [95% CI, −4.87 to 1.30]; *P* = .255) and week 8 (β = −2.58 [95% CI, −5.45 to 0.30]; *P* = .080) did not reach statistical significance. The MICE-pooled omnibus Group × Time interaction was significant (F[3, 5338] = 3.59; *P* = .013), indicating differential total fatigue trajectories between groups, driven primarily by the early advantage at week 2 Both groups demonstrated significant improvement in total fatigue over time (Time main effect: F[3, 9051] = 30.60; *P* < .001) **(Table 3 & Figure 3).**

Multiple Comparisons Correction. For all secondary outcomes, pairwise Group × Time interaction contrasts (k = 27) were adjusted for multiplicity using the Benjamini-Hochberg false discovery rate (BH-FDR) procedure. Outcomes achieving BH-corrected significance (*q* < .05) were: PPT at weeks 2 and 4; PSQI at weeks 4 and 8; HADS at weeks 4 and 8; MFI General Fatigue at weeks 2 and 4; and MFI Total Score at week 2.

All significant contrasts demonstrated large or moderate effect sizes (Cohen's *d* range: −0.66 to −1.86), with the exception of MFI Total at week 2 (*d* = −0.40, Small) **(Table 3).**

11 SENSITIVITY ANALYSIS, MNAR TIPPING POINT (PRIMARY OUTCOME)

To assess robustness of the primary outcome (NPRS Week 8) to departures from the missing-at-random (MAR) assumption, a tipping-point sensitivity analysis was conducted under a not-missing-at-random (MNAR) framework. Dropouts were re-imputed with a systematic perturbation δ applied adversarially (DN+IMS withdrawers [n = 5] shifted +δ points worse; DN withdrawers [n = 8] shifted −δ points better) at values from δ = 0 to 5.0 NPRS points in 0.25-point increments. Statistical significance was maintained through δ = 1.25 (*P* = .047), with the tipping point reached at δ = 1.50 (*P* = .071). As δ = 1.50 corresponds to the lower bound of the NPRS MCID (1.5–2.0 points), a systematic departure from MAR exceeding the minimally clinically important difference would be required to nullify the treatment effect, supporting the robustness of the primary conclusion. Under the favourable scenario, significance was maintained at all perturbation levels through δ = 5.0 **(Supplementary Figure 1 & Supplementary table 2)**.

12 DISCUSSION

In this randomized controlled trial, adults with fibromyalgia receiving dry needling combined with intramuscular electrical stimulation (DN+IMS) demonstrated greater improvements in pain intensity, sleep quality, and mood symptoms compared with dry needling alone, with effects that were statistically significant and clinically meaningful at the 8-week follow-up. Improvements in mechanical pain sensitivity were significant during the active treatment phase but attenuated by follow-up, suggesting a time-limited advantage in pressure pain threshold modulation. Treatment effects on fatigue were selective rather than global, with significant between-group differences observed for general fatigue and total fatigue score during or shortly after the active treatment phase, but not consistently across all MFI-20 domains or timepoints. Across most outcomes, between-group separation was more pronounced at later timepoints,

particularly weeks 4 and 8, than at the early week 2 assessment, suggesting that the therapeutic advantage of adding electrical stimulation to dry needling accrues progressively rather than emerging acutely. Taken together, these findings indicate a potential benefit of intramuscular electrical stimulation as an adjunct to dry needling in fibromyalgia, while also reflecting the complexity of achieving consistent, broad-spectrum symptom modulation in this condition.

12.1 Pain

Pain reduction is a central therapeutic objective in fibromyalgia management. Participants receiving DN+IMS demonstrated significantly lower Numeric Pain Rating Scale (NPRS) scores at Week 8 compared with DN alone (β = −1.20; 95% CI, −2.04 to −0.36; p = .005; Cohen's d = −1.11, Large), representing the pre-specified primary confirmatory contrast. This effect was consistent across the treatment period, with significant between-group differences also observed at Week 2 (β = −1.00; p = .020) and Week 4 (β = −1.26; p = .004), indicating a sustained and progressive pain reduction advantage for DN+IMS. The tipping-point sensitivity analysis demonstrated that a systematic departure from the missing-at-random assumption exceeding 1.50 NPRS points, equivalent to the lower bound of the minimally clinically important difference, would be required to nullify the primary finding, supporting the robustness of this conclusion. This magnitude of change exceeds the commonly accepted minimal clinically important difference (MCID) threshold of 1.0 point for chronic pain trials [28], supporting clinical relevance. Improvements were observed over time in both groups, but the between-group difference was most clearly evident at follow-up rather than consistently across earlier time points. These findings are broadly consistent with prior randomized trials and systematic reviews reporting moderate reductions in pain following dry needling in fibromyalgia [3, 13]. The present study extends this evidence by suggesting that adjunctive electrical stimulation may modestly enhance analgesic response, particularly in sustaining effects through follow-up. Nevertheless, because interaction effects were not uniformly significant at intermediate time points, temporal superiority should be interpreted cautiously.

12.2 Pressure pain threshold

Objective measures of mechanical pain sensitivity favoured the DN+IMS approach during the active treatment phase. PPT scores were significantly higher in the DN+IMS group at Week 2 (β = 0.46; 95% CI, 0.30–0.61; $p < .001$; Cohen's $d = +2.18$, Large) and Week 4 (β = 0.35; 95% CI, 0.15–0.55; $p < .001$; $d = +1.28$, Large), indicating substantially greater tolerance to mechanical stimulation during treatment. At Week 8, DN+IMS scores remained numerically higher (2.61 vs 2.32 kg/cm²; $d = +0.74$, Moderate); however, this difference did not reach statistical significance under the full ITT MICE-pooled analysis (β = 0.19; 95% CI, −0.04 to 0.42; $p = .100$; BH-adjusted $q = .169$). The significant Group × Time interaction across the observation period ($F[3, 6232] = 12.74$; $p < .001$) confirms that the two groups followed meaningfully different trajectories, with the benefit of DN+IMS concentrated in the active treatment phase. The attenuation of the PPT advantage at follow-up may reflect partial regression toward baseline sensitivity after treatment cessation and warrants investigation in trials with extended follow-up. Systematic review evidence indicates moderate standardized effects of dry needling on PPT in fibromyalgia patients [13]. The persistent and large between-group contrast observed during the active treatment phase in this study, particularly the Week 2 effect size of $d = +2.18$, suggests a possible additive neuromodulatory effect of electrical stimulation beyond that achieved by dry needling alone, consistent with proposed mechanisms of intramuscular electrical stimulation on central sensitisation and descending inhibitory pathways. Nevertheless, PPT measurements are methodologically variable and susceptible to participant expectation effects, and the absence of direct neurophysiological biomarkers limits mechanistic interpretation of these findings [13].

12.3 Sleep quality

Sleep disturbance is a pervasive feature of fibromyalgia and contributes to central sensitisation and symptom amplification. At baseline, PSQI scores were comparable between groups (DN+IMS, 13.51 [SD, 2.46] vs DN, 13.44 [SD, 2.00]; $p = .880$), confirming equivalent sleep impairment at randomisation. The between-group difference at Week 2, while directionally consistent with a treatment advantage for DN+IMS (β =

−1.01; 95% CI, −2.39 to 0.38; $p = .153$; Cohen's $d = −0.40$, Small), did not reach statistical significance, suggesting that sleep improvements accrued progressively over the treatment course rather than emerging acutely. Significant and clinically meaningful between-group differences were observed at Week 4 (β = −2.52; 95% CI, −3.90 to −1.14; $p < .001$; BH-adjusted $q = .002$; $d = −1.61$, Large) and were sustained at Week 8 (β = −2.63; 95% CI, −4.01 to −1.24; $p < .001$; $q = .002$; $d = −1.33$, Large), with DN+IMS group mean scores of 8.79 and 8.69 respectively compared with 11.70 and 11.74 in the DN group. The omnibus Group × Time interaction confirmed significantly differential trajectories between groups across the observation period ($F[3, 11838] = 7.99$; $p < .001$). The magnitude of reduction in the DN+IMS group from baseline to Week 8 (approximately 4.82 points) exceeds the commonly cited MCID threshold of approximately 3 points for the PSQI total score, suggesting meaningful clinical improvement beyond statistical significance. Previous dry needling trials have reported modest improvements in sleep parameters[13, 14]; the substantially larger effect sizes observed here, particularly the large effect maintained through the 8-week follow-up, may reflect enhanced neuromodulatory input through the addition of electrical stimulation, potentially modulating the hypothalamic-pituitary-adrenal axis dysregulation and autonomic dysfunction that underpin sleep pathology in fibromyalgia. However, sleep outcomes are influenced by behavioural, psychological, and environmental factors, and improvements cannot be attributed solely to nociceptive modulation. These findings should therefore be interpreted within the broader biopsychosocial context of fibromyalgia.

12.4 Mood symptoms

The magnitude of mood improvement observed with DN+IMS was statistically significant and clinically meaningful. ITT MICE-pooled estimates indicate that the DN+IMS group demonstrated a reduction of approximately 7.36 points on the Hospital Anxiety and Depression Scale (HADS) from baseline to Week 8 (21.26 to 13.90), compared with a reduction of approximately 3.57 points in the DN group (21.03 to 17.46). The Week 2 between-group difference, while directionally consistent (β = −1.88; 95% CI, −3.92 to 0.15; $p = .070$; Cohen's $d = −0.52$, Moderate), did not reach statistical

significance, indicating that mood benefits accrued progressively rather than emerging acutely. Significant between-group differences were observed at Week 4 (β = −2.70; 95% CI, −4.74 to −0.66; p = .010; BH-adjusted q = .034; d = −0.84, Large) and were largest at Week 8 (β = −3.17; 95% CI, −5.21 to −1.13; p = .002; q = .008; d = −1.29, Large). The omnibus Group × Time interaction confirmed significantly differential trajectories (F[3, 11794] = 4.48; p = .004). Published MCID values for the HADS total score range from 1.5 points per subscale to approximately 3.0 points for the total score in chronic disease populations (Puhan *et al*., 2008; Lemay *et al*., 2019); the between-group difference of 3.17 points at Week 8 meets or exceeds this threshold, supporting clinical as well as statistical significance. Crucially, the observed effect size of d = −1.29 at Week 8 represents a large standardized effect, substantially larger than the approximate $d \approx 0.7$–0.8 previously assumed under typical HADS variability, reflecting both the magnitude of improvement in the DN+IMS group and the precision afforded by the full ITT analysis [29, 30]. However, given that the Week 2 group × time contrast did not reach significance, and that psychological outcomes in fibromyalgia are susceptible to multifactorial contextual influences including expectation effects, sleep improvement, and pain reduction, these findings should be interpreted with appropriate caution. Overall, the data suggest that the addition of intramuscular electrical stimulation to a dry needling programme may confer meaningful additional benefit in reducing anxiety and depressive symptoms, though confirmation in larger and methodologically diverse samples is warranted [31, 32].

12.5 Fatigue

Fatigue in fibromyalgia is multidimensional and often resistant to intervention. In this trial, MICE-pooled ITT analysis with unstructured covariance demonstrated significant Time effects across all MFI-20 domains (all $p < .001$), indicating that both groups improved in fatigue over the observation period. Treatment-specific effects, however, were selectively observed.

For General Fatigue, significant between-group differences favouring DN+IMS emerged as early as Week 2 (β = −0.66; 95% CI, −1.04 to −0.29; $p < .001$; BH-adjusted q = .003; Cohen's d = −0.68, Moderate) and were greatest at Week 4 (β = −1.33; 95% CI,

−1.71 to −0.95; $p < .001$; $q < .001$; $d = -1.86$, Large), representing a large and clinically meaningful treatment-specific effect during the active treatment phase. At Week 8, the between-group difference attenuated and did not reach statistical significance ($\beta = -0.55$; $p = .081$; $q = .150$; $d = -0.33$, Small), suggesting that the General Fatigue advantage of DN+IMS may partially regress following treatment cessation, a pattern consistent with the PPT findings and warranting investigation in trials with booster sessions or extended follow-up.

For Total Fatigue score, a significant between-group difference was identified at Week 2 ($\beta = -2.16$; 95% CI, −3.83 to −0.49; $p = .011$; $q = .034$; $d = -0.40$, Small), a finding that was not apparent under the prior complete-case analysis, with the omnibus Group × Time interaction confirming differential trajectories ($F[3, 5338] = 3.59$; $p = .013$). Between-group differences at Weeks 4 and 8 did not reach significance, indicating that the total fatigue advantage was most pronounced early in the treatment course.

For Reduced Motivation, the MICE-pooled omnibus Group × Time interaction reached statistical significance ($F[3, 5346] = 3.14$; $p = .024$), indicating a detectable multivariate pattern difference in trajectories between groups. However, no individual timepoint contrast achieved FDR significance (all $q > .15$) and effect sizes were consistently trivial to small, limiting clinical interpretation of this finding.

Physical Fatigue (omnibus GxT $p = .061$), Mental Fatigue ($p = .660$), and Reduced Activity ($p = .280$) showed no significant Group × Time interactions, with all individual contrasts trivial in effect size, indicating that these dimensions of fatigue responded equivalently in both groups. This pattern aligns with systematic reviews concluding that dry needling demonstrates stronger evidence for pain reduction than for global fatigue modulation [21, 33]. The heterogeneous response across MFI-20 domains likely reflects the multifactorial aetiology of fatigue in fibromyalgia, encompassing sleep disturbance, mood dysfunction, physical deconditioning, and metabolic influences. The selective treatment effect on General Fatigue and early Total Fatigue, rather than across all fatigue dimensions, may suggest that the neuromodulatory mechanisms of DN+IMS preferentially target fatigue components most closely linked to pain and central sensitisation. Although selected fatigue domains demonstrated clinically meaningful change, broader generalisation should be approached cautiously, and these secondary

findings should be considered hypothesis-generating pending replication in adequately powered trials [34-36].

The additive therapeutic effects observed with DN+IMS may reflect complementary and potentially synergistic neurophysiological mechanisms. Dry needling is proposed to modulate dysfunctional motor endplate activity, reduce peripheral nociceptive sensitisation, and elicit local twitch responses that disrupt self-sustaining myofascial trigger point cycles [37]. Intramuscular electrical stimulation may augment these effects through additional recruitment of Aβ and Aδ afferent fibers, activation of segmental spinal inhibitory interneurons, and engagement of descending inhibitory pathways via periaqueductal grey and rostroventromedial medullary projections[38-40]. This convergent peripheral and supraspinal input could account for the large treatment-specific effects on pressure pain threshold and pain intensity observed during the active treatment phase, as well as the progressive accrual of benefits in sleep and mood, outcomes that are closely linked to dysregulation of the hypothalamic-pituitary-adrenal axis and autonomic nervous system in fibromyalgia. The attenuation of the PPT advantage and general fatigue benefit at the 8-week follow-up, following treatment cessation, is consistent with the view that sustained neuromodulatory effects may require ongoing stimulation, and raises the question of whether maintenance sessions or higher-frequency protocols could preserve these gains. However, all mechanistic interpretations in the present study remain speculative, as no neurophysiological measurements, inflammatory biomarkers, or central sensitisation indices were obtained. Future trials incorporating such assessments alongside patient-reported outcomes would substantially strengthen the evidence base for the proposed mechanisms [40].

12.6 Strengths and limitations

The strengths of this study include randomized allocation, a complete intention-to-treat analysis (N = 78) using multiple imputation by chained equations (MICE; M = 50), covariance-structure selection via MICE-pooled AIC, omnibus testing via Li-Meng-Rubin pooled Wald F-statistics, Benjamini-Hochberg false discovery rate correction across all 27 secondary contrasts, and a formal MNAR tipping-point sensitivity analysis for the primary outcome. Several endpoints met MCID criteria, adding clinical

significance beyond statistical significance. Large effect sizes (Cohen's $d > 0.80$) were observed for NPRS, PPT, PSQI, HADS, and MFI General Fatigue at key timepoints.

The limitations of this study include a relatively small sample size, underrepresentation of male participants, inherent difficulties in blinding intervention-based treatments, and the absence of mechanistic biomarkers. Although missing data were handled via a principled ITT framework under the missing-at-random (MAR) assumption, some withdrawals were attributable to insufficient therapeutic response or treatment intolerance, raising the possibility that some data were not-missing-at-random (MNAR). The tipping-point sensitivity analysis for the primary outcome demonstrated that a departure from MAR exceeding the MCID lower bound ($\delta = 1.50$ NPRS points) would be required to nullify the primary finding, supporting robustness; however, similar formal MNAR sensitivity analyses were not conducted for secondary outcomes, and longitudinal estimates for those outcomes should be interpreted with this limitation in mind. Furthermore, while the omnibus Group × Time interaction was significant for several outcomes (NPRS, PPT, PSQI, HADS, MFI General Fatigue, MFI-RM, MFI Total), the pattern of significance at individual timepoints varied, most notably, the PPT advantage was concentrated in the active treatment phase and was non-significant at Week 8, and MFI General Fatigue showed significance at Weeks 2 and 4 but not Week 8. Secondary outcomes should be considered hypothesis-generating and interpreted in the context of the multiplicity-corrected findings.

13 CONCLUSION

In this randomized clinical trial, the addition of intramuscular electrical stimulation to dry needling resulted in greater improvements in pain intensity, mechanical pain sensitivity, sleep quality, and mood symptoms compared with dry needling alone, with effects that were clinically meaningful and sustained at the 8-week follow-up. Improvements in fatigue were observed in both groups over time; however, treatment-specific benefits were selective, primarily involving general fatigue during the active treatment phase rather than across all fatigue dimensions. These findings suggest that intramuscular electrical stimulation may augment the therapeutic response of dry needling in fibromyalgia, particularly for pain, sleep, and mood, though the magnitude

and durability of benefit varied across symptom domains. The superiority of the combined approach was most consistently evident toward the end of the follow-up period rather than uniformly across all stages of treatment. Replication in larger, methodologically diverse samples with extended follow-up is warranted to confirm these findings and to clarify the durability and mechanisms of the observed treatment effects.

DECLARATIONS

- Ethical Approval: The study was reviewed and approved by the Research Ethical Committee, University of Lahore (REC-UOL-/572/08/24; dated 12-04-2024).
- Informed Consent: Written informed consent was obtained from all participants prior to inclusion in the study. In compliance with ethical standards, the study adhered to the principles of the Declaration of Helsinki.
- Consent for Publication: Not Applicable
- Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.
- Competing Interest: The authors declare that they have no competing interest.
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Authors' Contribution

Concept: MAA.

Design: UA.

Data Collection: MAA, MS

Analysis: AA.

Supervision & Critical Review: UA, NK

Drafting: UA, MAA

Data availability

All datasets relevant to this study's findings are fully available within the article.

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