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Original Research Article

Preventive Analgesia with Pregabalin in Neuropathic Pain from "Failed Back Surgery Syndrome": Assessment of Sleep Quality and Disability

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Abstract

Objective. Pregabalin group (PGB) is an antiepileptic used to treat neuropathic pain. We evaluated analgesic efficacy and safety for postoperative/chronic pain, disability, and sleep quality in patients who underwent spine surgery administered with PGB, or not, during the presurgical and postsurgical periods.

Design. Retrospective cohort study of 60 patients (two groups with 30 patients) with full information on 50 (29 with PGB and 21 without PGB). Ten patients were dismissed as information was lacking. The PGB group (P) (29 patients) received 75 mg/12 hours before surgery, 150 mg 10 hours after surgery, and 150 mg/12 hours 3 days after surgery. The control group (C; 21 patients) took no PGB.

Methods. Neuropathic pain was assessed before surgery, and 2 and 6 months later using visual analog scales (VAS), DN4, disability (Oswestry), and sleep quality. No serious adverse events occurred with PGB.

Results. The median VAS pain score at rest was lower in the PGB group at 2 months postsurgery (1 vs 2, $P = 0.032$), as was the median DN4 score (0 vs 3, $P = 0.032$) and the median Oswestry disability index (ODI: 12 vs 18, $P = 0.001$). At 6 months postsurgery, pain scores were also lower in the PGB group for VAS (0 vs 4, $P = 0.001$), DN4 score (0 vs 4, $P = 0.001$) and the ODI (10 vs 24, $P = 0.001$). Improvement in the functionality and sleep quality of the PGB group was noteworthy ($P = 0.018$).

Conclusions. PGB has analgesic/antihyperalgesic effects on postoperative neuropathic pain after surgery for lumbar disc hernia. Our findings show that this benefit increases with time.

Key Words. Pregabalin; Analgesia; Neuropathic Pain; Spine Surgery; Postoperative Pain; Experimental

Introduction

Failed back surgery syndrome (FBSS) is a chronic pain condition with a considerable impact on patients and health care systems [1], and surgical back treatment is a frequent procedure in neurosurgical practice [2]. The number of spine surgeries has steadily increased in recent decades [1,3,4]. Despite the advances made in surgical and better patient selection technologies, FBSS is still a frequent painful entity which is complex and difficult to treat.

Very few management guidelines exist for patients with FBSS, mainly because it is a complex entity with diverse

underlying etiologies [5–7]. Neuropathic pain is the most difficult pain type to treat and is usually refractory to opioid and nonsteroidal anti-inflammatory drug treatment [8]. Furthermore, multiple (biological, psychological, and social) factors are involved in pain development, which requires an interdisciplinary management approach [9,10]. However in recent years, several trials have been designed to address the efficacy and appropriateness of patient management modalities. Comparisons of distinct treatment types have also been the objective of different studies.

After surgery, peripheral pain signals reach the central nervous system (CNS) through peripheral sensory fibers, mainly Aβ−type fibers (fast myelinated fibers associated with thermal and mechanical nociceptors) and C fibers (slow amyelinated fibers associated with polymodal nociceptors). When this stimulus is maintained due to trauma or surgery, a complex system of adaptive processes is activated. Activation starts in the dorsal horn of the medulla, this being the first synaptic station for pain signals. The neurotransmitters involved in modulating these signals are mainly glutamate and substance P.

The main analgesic drugs used for neuropathic pain are those that act by diminishing the production and generation of action potentials in A and C fibers by blocking voltage-dependent ion channels or helping the mechanisms that inhibit transmission of pain information along the spine [11].

Antiepileptic drugs have been used in pain management [12]. Rat models of neuropathic pain have suggested that Pregabalin (PGB) reduces neuropathic pain symptoms by inhibiting the release of glutamate in the spinal cord horn [13]. PGB acts by blocking voltage-dependent calcium channels and binds specifically and with a high affinity to the alpha-2-beta subunits of these channels (alpha-2-beta ligands) [14]. Nonetheless, the literature provides no clear evidence for beneficial effects of PGB in established acute postoperative pain [1,12].

We did this systematic review to assess the analgesic efficacy of perioperative PGB. The data were insufficient to reach conclusions about persistent pain, but the limited data available from two studies have suggested that PGB might be effective to reduce neuropathic pain. In conclusion, this review suggests that PGB improves postoperative analgesia compared with a placebo at the expense of increased sedation and visual disturbances [15].

The aim of this study was to evaluate the protective effects of PGB administered prior to surgery and during the postoperative period in patients undergoing spine surgery as a neuromodulator in pain. Disability, sleep quality, and adverse events were also evaluated.

Methods

This study was reviewed and approved by the Ethics Committee of the La Fe Polytechnic University Hospital in Valencia (east Spain), with approval number ACV-PRE-2014-01, where the study was conducted. The study was considered exempt from requiring informed consent as it was a secondary analysis of existing data contained in the hospital administrative datasets.

Source of Data

In the La Fe Polytechnic University Hospital, pain data are recorded as structured vital sign data in the electronic health record. These data are readily linked with outpatients and inpatient utilization.

Sample

Our goal was to identify a cohort of patients who underwent simple discectomies (open technique) in 2013, when a retrospective sample was conducted after reviewing the clinical records of all 280 patients who underwent discectomy. Of all these clinical histories, we selected the first 30 patients who received PGB before and after surgery according to a formal dosing regime (Group P), and the first 30 patients who did not receive PGB (Group C—the control group). It should be noted that there were no natural variations. All these 60 patients were operated by one of two surgeons, who both followed the same surgical technique (simple discectomies-open technique). All the patients underwent the same anesthetic technique, the only exception being use of PGB. Randomization was performed on all 60 patients in both Groups P and C by chronological order of surgery. In Group P, one patient was dismissed from the study due to lack of data tracking (2 or 6 months). In Group C, nine patients were dismissed due to lack of monitoring. This left 29 patients in group P (PGB) and 21 patients in Group C (no PGB). No patient (Group P + Group C) took PGB or opioids during the follow-up at 2 and 6 months (according to the exclusion criteria for this study).

The inclusion criteria were: 1) aged 18–69 years; 2) scheduled spine surgery; and 3) compliance with neuropathic pain criteria prior to surgery as per the DN4 questionnaire. The exclusion criteria were: 1) aged $\geq$80 years; BMI $>$ 40 kg/m^2; 2ii) intolerance of/hypersensitivity to any PGB component or to control treatment, acetaminophen and opiates; 3) history of alcohol or drug abuse; 4) use of anticonvulsant and/or antidepressant medication prior to surgery; 5) admission to the resuscitation unit due to complications following surgery; and 6) moderate to severe liver and/or kidney failure.

Data Collection

Patient characteristics and clinical data were collected from medical records. Pain evaluation was carried out according to the following schedule: 1) baseline evaluation prior to surgery and 2) a follow-up posttreatment evaluation at 2 months and 6 months.

Before surgery, all the patients were also instructed as to how to use a 10 cm (100 mm) visual analog scale (VAS) graded from 0 (no pain) to 10 (the most severe pain). Patients were also asked to assess if pain interfered with their daily activities and to complete the DN4 questionnaire to estimate probability of neuropathic pain [16]. The DN4 questionnaire was used by patients and their physicians. It contains 10 items (seven evaluated with questions and three obtained by examination). The total score was recorded, with each "yes" counting as 1 point and each no counting as 0 points. A patient score ≥ 4 indicated high probability of neuropathic pain. The Oswestry Disability Index (ODI) calculated the level of disability according to the following formula: total score (out of 50) $\times$ 100 = % of disability. An ODI score of 0–20% represents minimal disability; 21–40% denotes moderate disability; 41–60% means severe disability; 61–80% corresponds to a disabled individual; and 81–100% refers to a bedridden person. A three-level scale (good, fair, and poor) was used to measure sleep quality.

Adverse events were recorded on a structured questionnaire that listed the commonest adverse effects (headache, neck pain, nausea, vomiting, dizziness, scalp burning, hearing difficulties, cognitive changes, changes in levels of concentration, and mood changes) and included open-ended questions.

Treatments and Dose Rationale

Group P (PGB) was administered 75 mg of PGB (Lyrica, Pfizer) every 12 hours/day before surgery, 150 mg at 10 hours postsurgery, followed by 150 mg every 12 hours on the 3 days following surgery. This dose has been shown to significantly reduce pain in posttherapeutic neuralgia and painful diabetic neuropathy patients [17,18]. Group C did not receive PGB.

Statistical Analysis

Calculation of sample size was based on the presumption that the postoperative DN4 scores after the perioperative administration of 150 mg of PGB would be 3 when compared with 4.5 in group C, and with a standard deviation of 2.0 at all the time points, as observed in previous studies [16,17]. For the results to be of statistical significance with a type I error (α) of 5% and a power ($1-\beta$) of 0.80%, 19 patients had to be recruited in each group. To account for any dropouts, we identified 29 patients in group P (on PGB) and 21 patients in group C (not on PGB).

Data are presented as the median (IQR), mean (SD) or number of patients (%), whenever appropriate. To assess normality, Kolmogorov–Smirnov (K–S) tests were performed on the data set and stratified distribution plots were examined to verify the normality of the distribution of the continuous variables. Assumption of normality was rejected for most data. Consequently, data were compared with a nonparametric Kruskal–Wallis (K–W) test for independent samples.

Baseline characteristics were compared across treatment groups using two-way analysis of variance (ANOVA) or Fisher's exact test. Data on patient characteristics (age, weight, BMI, and pain history) were analyzed with two-way anovas for continuous variables and the chi-square test for categorical variables (gender, race, level of education, surgery site, initial symptoms, pain etiology, prior treatment, prior limitation, prior sleep quality). VAS pain scores, the ODI and sleep quality were also analyzed and comparisons were made at each time point by a Mann–Whitney rank-sum test for unpaired data. The incidences of side effects were analyzed by Fisher's exact test. Frequency of sleep quality was compared between the groups exposed and not exposed to PGB with the chi-square test ($P < 0.05$) at the baseline time, 2 months and 6 months. The software package SPSS 17.0 (SPSS Inc., Chicago, IL) was used for the statistical analysis. A P value <0.05 was considered significant.

Results

Fifty patients underwent spinal surgery, specifically disc hernia surgery, and prior neuropathic pain was evaluated during the study period. Of these patients, 58.0% were treated with PGB (group P, exposed to PGB) and 42.0% were not PGB (group C, not exposed to PGB). No differences in patient characteristics between both groups were found (Table 1). All the patients were submitted to the same treatment analgesic protocol after surgery: morphine (0.15 mg/kg/6 hours) and acetaminophen (1,000 mg/6 hours).

Pain type and location were reviewed, as were dominant symptoms, time since onset and treatment prior to surgery, as the basal characteristics (Table 2). This table shows that there were no significant differences in the previous clinical characteristics of both groups. In these two groups, the dominant symptoms were hyperalgesia and paraesthesia, and the dominant etiology was disc hernia with radiculopathy confirmed by electromyography. No patient in either group had previously received any anticonvulsant or antidepressant medication.

Table 3 and Figure 1 show that Group P (treated with PGB) presented a pain improvement (VAS) and reduced neuropathic pain (DN4 < 4); that is, neuropathic pain diminished over time and disappeared in Group P, but remained in the control group. The ODI was maintained, and even increased over time in Group P.

Table 4 shows the sleep quality results for the patients treated with PGB and those who were not, Sleep quality during the first few postsurgery days was better in Group C than in Group P: 14.3% of the patients in Group C vs 44.8% in Group P considered that their prior sleep quality was "poor" ($P < 0.02$). No differences

Table 1 Patient characteristics

Characteristics	Pregabalin Group (P) (N = 29)	Control Group (C) (N = 21)	*P* value
Age (years), mean (median; P 25th–75th P)	54.2 (10; 3–7)	47.7 (13; 22–72)	0.463
Female sex, mean ± SD	15 ± 57.7	11 ± 42.3	0.963
Body mass index (kg/m^2), mean (median; P 25th–75th)	26.6 (4.2; 24–30)	26.7 (2.7; 25–28)	0.918
Anthropometric weight (kg), mean ± SD	72.4 ± 14.1	76.0 ± 11.8	0.353
Race, N (%)			
Caucasian	25 (86.2)	19 (90.5)	0.457
South American	3 (10.3)	1 (4.8)	
North African	1 (3.4)	0 (0.0)	
Asian	0 (0.0)	1 (4.8)	
Level of education, N (%)			
Unknown	4 (13.8)	1 (4.8)	0.767
None	2 (6.9)	1 (4.8)	
Elementary	9 (31.0)	13 (61.9)	
Baccalaureate	9 (31.0)	2 (9.1)	
Graduate	5 (17.3)	4 (19.2)	

P 25th–75th = 25th–75th percentiles.
Data are expressed as number of patients (%75th percentiles). There were no significant differences between groups.

Table 2 Patient characteristics and clinical features

	Total (N = 50)	Pregabalin Group (P) (N = 29)		Control Group (C) (N = 21)		*P* value
	N	N	(%) or (Mean ± SD)	N	(%) or (Mean ± SD)	
Site						
Lumbar + LLs	35	20	57.1	15	42.7	0.210
Cervical + ULs	11	8	72.7	3	27.3	
LLs	1	1	100.0	0	0.0	
ULs	3	0	0.0	3	100.0	
Time with pain (months)	45	29	49.3 ± 43.8	20*	40.0 ± 23.0	0.423
Initial symptom						
Hyperalgesia + Paraesthesia	16	14	77.8	4	22.2	0.098
Paresis	2	2	100.0	0	0.0	
Hyperalgesia	12	5	41.7	7	58.3	
Paraesthesia	2	1	50.0	1	50.0	
Paresis + Paraesthesia	2	1	50.0	1	50.0	
Paresis + Hyperalgesia	1	1	100.0	0	0.0	
Paresis + Hyperalgesia + Paraesthesia	3	4	100.0	0	0.0	
Hypoaesthesia + Paresis + Paraesthesia	1	0	0.0	1	100.0	
Hypoaesthesia + Hyperalgesia	1	0	0.0	1	100.0	
Hypoaesthesia + Hyperesthesia + Paraesthesia	3	0	0.0	3	100.0	
LL Paraesthesia	1	1	100.0	0	0.0	
Hyperalgesia + Hypoaesthesia + Paraesthesia	1	0	0.0	1	100.0	
Hyperesthesia	1	0	0.0	1	100.0	

LLs = lower limbs; ULs = Upper limbs; SD = standard deviation.
Values are reported as mean (SD; range), median (25th–75th percentiles), and number of subjects, as indicated. There were no significant differences between groups.
*Information not contained in patient medical record.

Table 3 Clinical characteristics of individuals with controlled and uncontrolled pain with PGB and placebo and changes throughout the trial

	Pregabalin Group (P) Median (P 25th–75th)	Control Group (C) Median (P 25th–75th)	*P* value
Preoperative Oswestry score	36 (25–39)	26 (18–41)	0.845
Oswestry at 2 months	12 (4–20)	18 (12–26)	0.061
Oswestry at 6 months	10 (2–16)	24 (10–32)	0.001
Preoperative DN4 score	6 (4.0–6.5)	5 (3.5–6.0)	0.275
DN4 at 2 months	0 (0–2)	3 (2–4)	0.032
DN4 at 6 months	0 (0–2)	4 (3–5)	0.001
Preoperative VAS score	8 (6.5–9.0)	7 (5.58.0)	0.725
VAS at 2 months	1 (0–3)	2 (3–7)	0.032
VAS at 6 months	0 (0–4)	4 (2–5)	0.001

P 25th–75th = 25th–75th percentiles.
Values are reported as median (25th–75th percentiles).

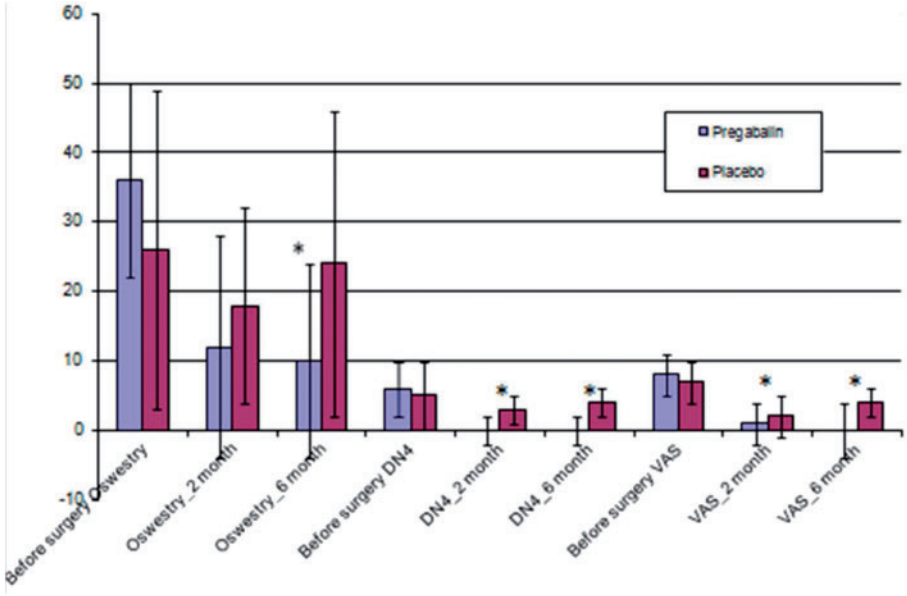

Figure 1 Pain scores: Oswestry, DN4, and VAS scores during the follow-up after treatment with placebo or pregabalin. Error bars represent the interquartile range from the median. *P value < 0.05 vs placebo by Mann–Whitney U test.

were observed in the scores obtained from the questionnaires administered to both groups (DN4, VAS, and ODI). An improvement was seen in the sleep quality assessment as 41.4% of the patients in Group P evaluated their sleep quality as "good" after 6 months, while 38.1% of Group C reported that their sleep quality was "good" for the same time interval ($P = 0.018$). No serious adverse events occurred with PGB.

Discussion

The new definition of *neuropathic pain* is "pain arising as a direct consequence of a lesion or disease that affects the somatosensory system," according to the NeuPSIG (Special Interest Group on Neuropathic Pain) [19,20]. Unlike nociceptive pain, which appears as a physiological response to tissue damage, neuropathic pain is an abnormal response to a lesion or disease in the somatosensory system.

It is known that surgical trauma induces hyperalgesia, which can help maintain postsurgery neuropathic pain [21], but it can reduce if we use PGB before surgery hyperalgesia.

Pain produced by degenerative spine diseases in general, and in the lumbar region in particular, is a frequent reason for consulting a physician. Most patients'

Table 4 Sleep changes in the trial with PGB and placebo

Pregabalin				Effect			Total
				Good	Fair	Poor	
Not exposed	Time	Baseline	N	10	8	3	21
			%	47.6	38.1	14.3	100.0
		2 months	N	9	6	6	21
			%	42.9	28.6	28.6	100.0
		6 months	N	8	7	6	21
			%	38.1	33.3	28.6	100.0
	Total		N	27	21	15	63
			%	42.9	33.3	23.8	100.0
Exposed	Time	Baseline	N	7	9	13	29
			%	24.1	31.0	44.8*	100.0
		2 months	N	8	13	8	29
			%	27.6	44.8	27.6	100.0
		6 months	N	12	13	4	29
			%	41.4	44.8	13.8	100.0
	Total		N	27	35	25	87
			%	31.0	40.2	28.7	100.0

*Indicates a level of significance of $P < 0.02$ between those not exposed and exposed to PGB for the baseline time for the poor effect group.
Data are expressed as number of patients (%). There were significant differences between the groups (P value = 0.018)

symptoms improve with only medical treatment, but some patients require surgery. Between 5% and 20% of patients do not improve after surgery, or even relapse during postsurgery year 1 [22]. Various factors are involved in pain relapse, which give rise to "failed back surgery syndrome" (FBSS). Although the pain type that appears in this syndrome is usually mixed (nociceptive and neuropathic), neuropathic pain is normally the type that causes most suffering and disability because of the complexities to diagnose and treat it.

The impact of FBSS on an individual's quality of life and functional status is considerable and more disabling compared with other common chronic pain conditions [12,23]. The finding that PGB is a therapeutic option emphasizes the importance of identifying new strategies to prevent FBSS from developing.

This study has proven the efficacy of PGB for neuropathic pain. Patients experienced substantial benefits with PGB, and there is evidence to support its use. These results correspond to a limited number of FBSS patients, who were compared with a group that was not exposed to PGB. More information is required to confirm these results given the small number of patients and the few studies conducted on this theme.

We herein show that PGB treatment can be a therapeutic option and can be held against the results which have shown that gabapentin has a minor beneficial effect on acute postoperative pain [24], but it is necessary to compare them.

Our data collected at 2 and 6 months also suggest that using perioperative PGB may be considered an alternative for preventing nerve-injury incident pain. Our study also identifies the association between using PGB before and 3 days after surgery with better ODI DN4 and VAS results at 6 months postsurgery, but further studies are needed to identify causality. Unlike other studies into PGB, we found no association in our patients of visual disturbance, nausea, vomiting, dizziness, or headache [15]. These results could be due to PGB being administered in this study for a short period of time.

The literature [12] provides no clear evidence for any beneficial effect of PGB on acute postoperative pain, but the above-cited study examined PGB in other situations (fibromyalgia, post-therapeutic neuralgia, painful diabetic neuropathy, and so forth.). Other authors have reported the efficacy of neuropathic pain conditions, but have also referred to adverse events, such as daily somnolence (15–25%) and dizziness (27–47%). We observed no adverse effects in our study, probably because we used PGB for a limited period of time (the perioperative period). Our use of PGB, therefore, differs from that indicated in those studies that involved a continuous or intermittent use of PGB. The dose we used was also lower than in other studies.

The development of new drugs with a mechanism of action that relates to the prevention or reduction of peripheral and central neuronal hyperexcitability induced by surgical procedures has given rise to the development of preventive analgesia for such pain [25]. This consists in administering drugs during the preoperative and immediate postoperative periods to reduce peripheral and central sensory responses to pain by interrupting the inflammation-hyperalgesia-increased pain stimulus cycle [26].

The pharmacological effects of PGBn are believed to result from its action as a ligand at the alpha-2-delta binding site, which is associated with the voltage-gated calcium channels in the CNS [27]. Potent PGB binding at the alpha-2-delta site has been shown to reduce the depolarization-induced calcium influx at nerve terminals, which consequently reduces the release of several excitatory neurotransmitters, including glutamate, norepinephrine, substance P, and CGRP [28,29]. It is likely that this modulation of neurotransmitter release by PGB contributes to the drug's anticonvulsant, analgesic, and anxiolytic effects. Animal models of surgical pain and clinical studies in adults have demonstrated that these conditions trigger allodynia and hyperalgesia, which are modified by gabapentin, independently of opioid receptor activation [36].

Very few randomized prospective clinical trials that have assessed the role of PGB in postoperative pain have been published in indexed journals to date [31,32]. Yet the outcomes achieved are promising in terms of pain relief [30], opiate use, and side effects following opiate use [33,34].

PGB has been shown to possess antiallodynic and antihyperalgesic activity in different neuropathic pain models, and to have a similar antinociceptive pain profile to that of gabapentin, but with a dose that is threefold to fourfold lower [35]. It is effective in models of mechanical allodynia, which is caused by a nerve lesion in surgery [36]

This Study Has Several Limitations

The sample "size" is limited, although the target was to mainly compare the two groups (with and without PGB), where differences were found. We could compare these groups better with a larger sample size.

It is a "retrospective" study, although patient monitoring was performed according to the same protocol in the same hospital. Prospective studies could provide us with better information.

In this study, we investigated the analgesic effect of postsurgical neuropathic pain with PGB to prevent subsequent chronicity. Future studies into this objective are necessary.

A first-line drug to treat neuropathic pain in the Practice Guidelines of the NeuPSIG (Special Interest Group on Neuropathic Pain) [34] and by the European Federation of Neurological Societies [37,38] has been herein considered.

The results obtained herein as regards pain improvement, disability, and sleep quality were better and statistically significant in Group P compared with Group C, and improvement even increased over time in Group P. The PGB tolerance profile was very good and no major side effects that would require the drug to be withdrawn were observed.

Conclusions

This is a retrospective cohort study which demonstrates that PGB has analgesic or antihyperalgesic effects on postoperative neuropathic pain for lumbar disc hernia. Our findings show that this benefit increases with time. More research is needed to corroborate our results.

Neuropathic pain is the most difficult pain type to treat and entails a high socioeconomic cost. The results of this study on the benefit of using PGB would be a breakthrough to start preventing FBBS neuropathic pain.

In addition to its potential effects on postoperative neuropathic pain, PGB may prove valuable as a tool to study acute neuropathic pain mechanisms. Further long-term studies are needed to confirm these promising results.

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