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Conditioned pain modulation predicts duloxetine efficacy in painful diabetic neuropathy

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ABSTRACT

This study aims to individualize the selection of drugs for neuropathic pain by examining the potential coupling of a given drug's mechanism of action with the patient's pain modulation pattern. The latter is assessed by the conditioned pain modulation (CPM) and temporal summation (TS) protocols. We hypothesized that patients with a malfunctioning pain modulation pattern, such as less efficient CPM, would benefit more from drugs augmenting descending inhibitory pain control than would patients with a normal modulation pattern of efficient CPM. Thirty patients with painful diabetic neuropathy received 1 week of placebo, 1 week of 30 mg/d duloxetine, and 4 weeks of 60 mg/d duloxetine. Pain modulation was assessed psychophysically, both before and at the end of treatment. Patient assessment of drug efficacy, assessed weekly, was the study's primary outcome. Baseline CPM was found to be correlated with duloxetine efficacy ($r = 0.628$, $P < .001$, efficient CPM is marked negative), such that less efficient CPM predicted efficacious use of duloxetine. Regression analysis ($R^2 = 0.673$; $P = .012$) showed that drug efficacy was predicted only by CPM ($P = .001$) and not by pretreatment pain levels, neuropathy severity, depression level, or patient assessment of improvement by placebo. Furthermore, beyond its predictive value, the treatment-induced improvement in CPM was correlated with drug efficacy ($r = -0.411$, $P = .033$). However, this improvement occurred only in patients with less efficient CPM (16.8 ± 16.0 to -1.1 ± 15.5, $P < .050$). No predictive role was found for TS. In conclusion, the coupling of CPM and duloxetine efficacy highlights the importance of pain pathophysiology in the clinical decision-making process. This evaluative approach promotes personalized pain therapy.

1. Introduction

Satisfactory relief of neuropathic pain is 1 of the most elusive goals in pain medicine. A major problem, common to non-neuropathic pain as well, is the lack of knowledge about which drug best suits a specific patient. This is particularly important because of the relatively low efficacy of these agents, leading to the common trial-and-error approach that entails a long and frustrating optimization process usually involving more than 1 drug.

Changes in pain modulation processes, as reflected by dynamic psychophysical tests, are now increasingly recognized as clinically relevant. Inhibition of experimental pain is tested at bedside by the conditioned pain modulation (CPM) protocol, where the administration of 2 simultaneous painful stimuli typically results in pain inhibition [20,29]. Decreased inhibition of experimental pain is found in many patients with idiopathic pain syndromes [6,13,14,16,17,19,21,22,24]. It is related to past history of and predicts future chronic pain [8,28]. Enhanced sensitization is also prevalent in idiopathic pain syndromes and has a predictive value for future pain [25]. This is tested by the temporal summation (TS) test protocol, where a train of stimuli of constant intensity is administered, with a typical increase in pain rating along the series. Patients exhibiting decreased inhibition and/or increased summation capacities are collectively described as having a 'pro-nociceptive' pattern of pain modulation.

In this study, we explore relevance of the pain modulation pattern for predicting responsiveness to neuropathic pain medication. Our hypothesis is that agents used for neuropathic pain should be prescribed by relating their mode of action to the specific individual's pattern of pain modulation. Thus, an agent that augments pain inhibition should be more efficacious in patients with less efficient endogenous pain inhibition than in those with efficient

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inhibition. Similarly, an agent that reduces neuronal sensitization should be more efficacious in patients with enhanced summation as compared to those with normal summation.

This hypothesis was examined using duloxetine, a serotonin-noradrenalin reuptake inhibitor (SNRI) agent, assumed to augment descending pain inhibition by inhibiting reuptake of spinal noradrenalin and serotonin [12,23]. We expected duloxetine to be more efficacious in patients characterized by decreased endogenous pain inhibition capacity, as expressed by less efficient CPM. In turn, we expected that TS would not be primarily associated with duloxetine efficacy, as SNRIs do not target neuronal sensitization.

The aim of the present study was to examine this hypothesis by application of static and dynamic psychophysical tests to predict the efficacy of duloxetine in patients with painful diabetic neuropathy. A further complementary step was to explore whether pain modulation patterns change in response to treatment, and whether any pain alleviation could be attributed to such a change.

2. Methods

2.1. Study population

A total of 30 patients with painful diabetic neuropathy and distal lower limb pain completed the study. Inclusion criteria were pain duration >3 months, and mean pain severity during the last month $\geqslant$40 on a numerical pain scale (NPS) of 0 to 100. Exclusion criteria were as follows: use of duloxetine or another SNRIs during the previous month; intake of a monoamine oxidase inhibitor (MAO-I) within the last 14 days; narrow-angle glaucoma; or inability to perform psychophysical testing. An institutional review board approved the use of human subjects for this study, and all participants signed an informed consent form. (The clinical trial identifier number is NCT01363284.)

2.2. Study design

Treatment consisted of 1 week of inactive placebo followed by 1 week of duloxetine 30 mg/d and then 4 weeks of duloxetine 60 mg/d. Two experimental sessions, pre- and post-treatment, were conducted by 1 experimenter (H.N.A.). The first was conducted within 1 week preceding the onset of treatment, and the second within a few days of treatment completion. A weekly phone follow-up was performed by the study nurse, in which patients were asked to rate the overall effect of the drug on their pain, a measure taken as drug efficacy, the main outcome measure of the study. They were also asked to rate the mean and maximal pain levels over the preceding week. The nurse and the patients were blinded to the sequence and relative length of drug/placebo use and to the baseline psychophysical results.

The first stage of the testing sequence in the experimental sessions consisted of static psychophysical measures of sensory and pain thresholds. This static testing stage was followed by the dynamic tests, including the CPM and the TS. The particular order of the various tests was randomized within the static and the dynamic study stages. Each patient underwent the same order of tests in both sessions. In addition to the psychophysical assessment, patients also self-reported their levels of clinical pain experience during the preceding week, relating to the mean and maximal pain levels. Since duloxetine is an antidepressant as well, the level of depression symptoms was obtained both before and after treatment.

2.3. Equipment

We used a TSA-II (Medoc, Ramat Yishai, Israel), which is a Peltier-based contact temperature stimulation device with a 30×30 mm^2 contact thermode. TSA-2001 was used for the assessment of cold and warm detection thresholds (CDT and WDT, respectively), for the assessment of heat pain threshold (HPT), and for delivering tonic heat pain serving as the 'test stimulus' in the CPM protocol.

von Frey Filaments (North Coast Medical, San Jose, California) were used to determine the mechanical detection and pain thresholds (MDT and MPT, respectively), magnitude estimation of suprathreshold mechanical pinprick pain, and mechanical temporal summation (mTS).

The water bath apparatus (Heto CBN 8-30 Lab equipment, Allerod, Denmark) used was a temperature controlled container, with a maximum temperature variance of ±0.5°C and continuous stirring action to ensure the maintenance of an even temperature throughout the bath. Hand immersion in the hot water bath served as a 'conditioning stimulus' in the CPM protocol.

2.4. Psychophysical assessments

The tests were performed after a short training session aimed at familiarizing the participants with the experimental protocol. To evaluate the level of neuropathy severity, WDT, CDT, and MDT were assessed at the dorsal foot. All pain psychophysical tests were performed at the volar aspect of the dominant forearm.

Thermal thresholds (CDT, WDT, and HPT) were assessed by the method of limits [27]. First, the thermode was attached and the skin was allowed to adapt to a temperature of 32°C. For the sensory threshold assessment, the thermode warmed or cooled at a slow rate (1°C/s) until the first warm or cold sensation pain was perceived. For the HPT, the temperature was increased at a rate of 2°C/s until the moment that the subject indicated the transition of the warm sensation into a painful heat. Each test was repeated 3 times, and the results were averaged to obtain the threshold value.

MDT and MPT were obtained using the von Frey filaments, which were applied perpendicular to the skin for 1 second, 3 times each in ascending order. The lowest-size filament that induced sensation was considered as the MDT, and the first filament that evoked pain was considered as the MPT.

CPM was performed using the parallel paradigm in which 2 identical noxious 'test stimuli' were delivered before to, and then simultaneously with, a noxious 'conditioning stimulus.' Contact heat applied to the volar forearm served as the 'test stimulus.' The intensity of the test stimulus was predetermined individually for each participant, based on the psychophysical parameter of *pain-60*, which is the temperature that induces pain ratings of 60 on an NPS of 0 to 100 [9]. The baseline temperature was 32°C, with increase and decrease rates of 2°C/s. Patients were asked to rate the level of pain intensity of the 'test stimulus' every 10 seconds (overall 4 pain reports). After a 15-minute break, the non-dominant hand was immersed in the hot water bath (up to the wrist) at 46.5°C for 60 seconds. During the last 30 seconds of this immersion, the 'test stimulus' was repeated, and the level of pain intensity experienced was rated again. The CPM effect was calculated as the difference (last minus first) in the average pain scores of the 2 'test stimuli.' A negative value indicated efficient CPM. This paradigm of conditioned pain modulation is routinely used in our laboratory [10,18,25,28]. The mean pain score of the stand-alone 'test stimulus' pain also served as a measure of supra-threshold tonic heat pain.

mTS was measured using the 180gr (# 6.45) von Frey filament. Patients were exposed to a single stimulus and then to 10 repetitive stimuli with an inter-stimulus interval (ISI) of 1 second applied within an area 1 cm in diameter. They were asked to rate the level of pinprick pain intensity using NPS for the single stimulus and then for the last stimulus of the train. The difference

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between the last and the first pain scores was calculated as the mTS score. The pain score for the first stimulus also served as a measure of suprathreshold mechanical pinprick pain.

2.5. Assessment of depression

Self-reported depression symptoms were evaluated by the Beck Depression Inventory (BDI) [4]. The BDI consists of 21 questions, rated from 0 to 3 in terms of intensity. The questionnaire assesses both the cognitive/affective and neurovegetative symptoms of depression. Patients are asked to circle the statement that best describes how they felt in the past week, including today. Total scores range from 0 to 63. The level of depression was assessed twice, once before and once at the end of the treatment.

2.6. Statistical analysis

Analyses were performed using JMP and SPSS (SPSS Inc., Chicago, IL). The main outcome measure was defined as the patient's rating of duloxetine's efficacy, defined as the extent of and the secondary outcome measure was the percentage of reduction in maximal pain scores. These measures were comprised of the mean of the 2 reports obtained during the last 2 weeks of treatment. The first stage of data analysis was to explore the associations between each of the independent variables, such as the experimental and clinical pain measures, as well as the depression scores and drug efficacy, using Pearson correlations matrix with Bonferroni correction. Consequently, a linear regression model was used to determine the relative contribution of the relevant study variables in the prediction of duloxetine's analgesic efficacy. ANOVA was used to examine the second study question of whether treatment modified the independent variables, and if yes, whether such a change was associated with the treatment efficacy.

3. Results

Of the 33 patients (8 female and 25 male, 60.2 ± 10.4 years of age) who enrolled in the study, 30 completed both experimental sessions. The mean diabetes duration was 13.9 ± 10.0 years. The mean duration of sensory symptoms was 4.2 ± 4.9 years, and the mean duration of neuropathic pain was 4.6 ± 6.5 years. The means for pretreatment foot WDT, CDT, and MDT were 44.4 ± 4.5°C, 22.4 ± 9.6°C, and 4.23 ± 0.10 # of Semmes–Weinstein logarithmic force scale respectively. The mean and maximal intensity of pain for the week preceding treatment were 63.3 ± 20.1 NPS and 75.4 ± 23.8 NPS, respectively.

Mean and maximal pain ratings were not associated with any of the static or dynamic psychophysical measures. A positive correlation was found between the 2 dynamic tests, CPM and mTS, such that less efficient CPM was associated with enhanced TS (r = 0.439, P = .015). As for the correlation between the dynamic and static psychophysical measures, MDT was the only parameter found to be correlated with CPM efficiency (r = −0.594, P < .006), such that patients with less efficient CPM had less severe large-fiber neuropathy.

Table 1
Clinical characteristics, experimental pain parameters, and pain-related personality factors before and after treatment.

Variable	Pretreatment	Post-treatment	P value
Neuropathic pain scores			
Mean clinical pain	63.3 ± 20.1	42.6 ± 29.9	.001
Max clinical pain	72.9 ± 20.6	47.4 ± 33.4	.001
Parameters of neuropathy severity			
WDT foot, °C	44.4 ± 4.5	43.8 ± 4.6	.449
CDT foot °C	22.4 ± 9.6	22.8 ± 9.8	.779
MDT foot, #	4.2 ± 0.1	4.3 ± 0.9	.868
Pain psychophysics			
MPT filament #	5.89 ± 0.78	5.89 ± 0.94	.980
HPT, °C	43.1 ± 4.1	42.5 ± 4.4	.329
Mean tonic pain	51.6 ± 18.4	49.2 ± 18.4	.142
Mean CPM	0.2 ± 22.9	−5.8 ± 15.9	.536
1st Mechanical pain	19.5 ± 23.1	14.6 ± 18.6	.180
mTS	12.6 ± 25.29	7.0 ± 19.1	.179

3.1. Drug use

Patients' mean self-report of drug efficacy was 57% ± 33 (range 2%–100%). Mean and maximal weekly pain levels were reduced significantly in response to the treatment (Table 1). Reports on drug efficacy at the end of the placebo week averaged 26% ± 26%. As for side effects, 7 patients reported constipation, 3 reported tiredness, and 2 had decreased appetite. Three patients did not complete the protocol because of sleepiness. At the end of the trial, patients were referred back to their treating physician for continuation of their treatment. It is noted that 47% of the patients expressed their wish to continue treatment with duloxetine.

3.2. Prediction of drug efficacy

The most important finding of this study is that pretreatment CPM efficiency was correlated with drug effect, such that less efficient CPM predicted better drug efficacy (r = 0.628, P < .001; Fig. 1). The linear regression analysis model (R^2 = 0.673; P = .012) revealed that after controlling for initial clinical pain, pretreatment level of depression, neuropathy severity as reflected by foot WDT and MDT, and the placebo effect, only pretreatment CPM magnitude predicted duloxetine efficacy (P = .001; Table 2).

The second outcome measure, that is, the extent of pain reduction, was also correlated with pretreatment CPM (r = 0.436, P = .023), as less efficient CPM was associated with greater pain reduction. In contrast to the predictive role of CPM, the mTS magnitude was not found to be associated with drug effect (r = 0.013, P = .537 or with the extent of pain reduction (r = 0.279, P = .150).

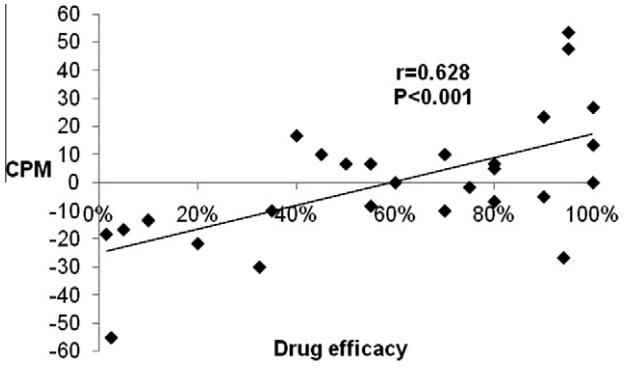

Fig. 1. Drug efficacy and pretreatment CPM. Patients with less efficient CPM (positive scores) reported higher drug efficacy and vice versa.

Table 2
Linear regression model for the prediction of duloxetine efficacy.

Predictor	B Coefficient	Beta	t	P
Pretreatment level of depression	1.08	0.27	1.45	.171
Initial clinical pain	0.29	0.24	1.03	.321
Foot MDT	5.53	0.16	0.74	.473
Foot WDT	−2.03	−0.24	−1.27	.227
Placebo effect	−0.23	−0.14	−0.63	.539
Pre-treatment CPM	1.16	0.822	4.20	.001

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In addition to the calculation of CPM efficiency based on an average of the 3 pain ratings obtained over the course of the 'test stimulus' administration, we also calculated CPM based on the pain scores obtained at either 10, 20, or 30 seconds after stimulus onset. Similar to the above-mentioned findings, patients with less efficient CPM at 10 and 20 seconds, but not at 30 seconds, demonstrated greater drug efficacy (r = 0.494, $P = .010$ and r = 0.601, $P < .001$, respectively).

Because duloxetine is an antidepressant agent as well, we examined whether pain-related drug efficacy could also be partially attributed to mood changes. As expected, the BDI scores were reduced in response to duloxetine treatment (from 13.0 ± 8.5 to 10.3 ± 9.0, $P = .009$). However, the extent of this reduction was not correlated with pain-related drug efficacy (r = −0.261, $P = .179$).

3.3. Plasticity of pain modulation under duloxetine

Static and dynamic experimental pain parameters, as well as nonpainful sensory detection thresholds before and after treatment, are detailed in Table 1. No significant change was observed for any of these parameters. Nevertheless, as less efficient pretreatment CPM predicted the response to duloxetine, we examined the correlation between CPM improvement and drug efficacy (Fig. 2). The results showed that greater improvement in CPM was associated with higher drug efficacy (r = −0.411, $P = .033$). A possible explanation for this moderate strength of correlation, and for the previously mentioned lack of significant change in CPM efficiency, is that there were 2 subgroups of patients. Therefore, further analyses were performed by median-split of the patients based on pretreatment CPM-efficiency. Results revealed a significant interaction between these 2 subgroups and treatment effect (pre, post, $P = .001$). The CPM improvement was observed only in those patients with inefficient pretreatment CPM Tukey Honestly Significant Difference (HSD), $P < .050$; Fig. 3).

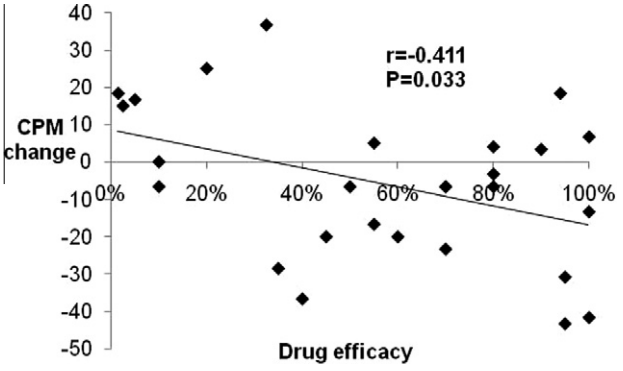

Fig. 2. Change in CPM by duloxetine. Higher benefit from the drug is paralleled by improved CPM efficiency (lower scores).

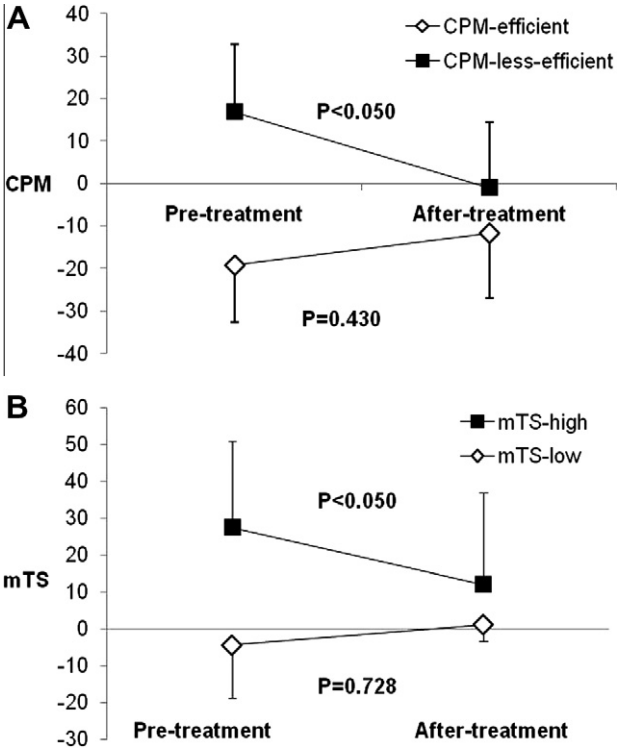

Fig. 3. Population-specific reversal of pro-nociception. Based on corresponding median split, only the patients with less efficient CPM (A) and enhanced mTS (B) significantly reversed these pro-nociceptive patterns.

Although mTS did not correlate with drug efficacy (r = −0.059, $P = .759$) and did not change after treatment, its pretreatment magnitude was positively correlated with CPM. Therefore, we examined mTS-based median-spilt grouping based on this measure. A significant interaction between group and treatment effect (pre, post, $P = .008$) was found, such that only those with high pretreatment mTS magnitude demonstrated a significant mTS reduction (Tukey HSD, $P < 0.050$).

4. Discussion

Our main finding is that pretreatment CPM efficiency measured in painful diabetic neuropathy patients predicts the efficacy of duloxetine. Patients expressing lower pain inhibitory capacity, as reflected by less efficient CPM, are likely to benefit from the drug, whereas those with efficient CPM are not. As expected, the other dynamic pain modulation parameter, mTS, was not found to predict duloxetine efficacy. Furthermore, we have shown that CPM can be modified in response to treatment. Although it improved along with pain alleviation by duloxetine in patients with less efficient pretreatment CPM, there was no change if CPM was efficient at baseline.

Drugs for neuropathic pain are well characterized, and the considerations in their administration have been well formulated in several guideline papers published in recent years [2,3,5,7,11]. Yet, when clinical circumstances necessitate selecting a drug for a specific patient, the recommended factors of pain etiology, severity, and physician experience do not identify the efficacious drug or drugs suitable for the individual patient. The common practice is a trial-and-error approach in choosing between 2 or more agents, which is a process that can take several months before pain is satisfactorily alleviated, if at all.

Our rationale in trying to improve the drug selection process stems from the inter-individual variability in patients' pain modulation patterns, as expressed by psychophysical test paradigms. Patients expressing a 'pro-nociceptive' pattern of modulation, such as less efficient CPM, are more likely to experience pain [28] or to belong to an idiopathic pain syndrome group [30]. As such, altered pain modulation patterns seem to be a significant pathophysiological factor contributing to pain generation. Following this line of thinking, we hypothesized that if an individual's pain modulation mechanism, such as CPM, is malfunctioning, then a drug that rectifies the mechanism would be most beneficial in alleviating the pain. Thus, we expected patients with less efficient CPM to benefit more from the SSNRI than those with well-functioning CPM.

Although not examined in this study, a similar set of considerations can be applied to pro-nociception represented by higher pain sensitization, as expressed by enhanced temporal summation. It would be expected that drugs reducing sensitization, such as the

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calcium α2δ channel ligands, gabapentin, and pregabalin, would be more efficacious in highly sensitized patients expressing enhanced TS than in those expressing lower TS. These agents have already been shown to be capable of reducing TS [1].

Theoretically, one could contemplate a converse scenario in which the pro-nociceptive pattern could reflect an irrecoverable deficit in 1 of the components of the pain modulation system, such as a receptor or channel, which medication cannot overcome. Accordingly, those patients who show a normal nociceptive pattern, that is, efficient inhibition or normal sensitization, would exhibit especially robust drug efficacy by further augmentation of the already functioning pain modulation mechanism, as manifested by increased pain inhibition.

Our results provide support for the first hypothesis that a drug is more efficacious in a pro-nociceptive pattern. The findings show that neuropathic pain is efficaciously treated by duloxetine in those with less efficient CPM, and vice versa. A short and simple test of pain modulation can thus indicate whether the SNRI family of drugs is likely or unlikely to benefit an individual patient. These findings open the door to individualized therapy for neuropathic pain patients. By coupling between a specific patient's pain modulation pattern and a specific drug's efficacy, the present study advances clinical pain medicine toward achieving the long-awaited goal of tailored treatment based on individual pain processing.

The present study also has an impact on the question of plasticity of the pain modulation pattern. The many studies showing pronociception to be common in idiopathic pain patients and to have predictive power for future postoperative pain imply that CPM and TS patterns are characteristics of these patients and therefore should be stable traits of neural processing, remaining more or less steady over time. This concept seems to be at odds with the remarkable plasticity demonstrated for the pain processing system at large, for example its short-term sensitization in response to painful stimuli [26]. Furthermore, a single study by Kosek and Ordenburg examined the long-term plasticity of CPM in patients and found that osteoarthritis patients exhibited improvements in CPM along with pain alleviation after hip surgery [15].

Our study further strengthens this concept by demonstrating changes in CPM and mTS with treatment. However, the change in both modulatory parameters is selective, with improvement evident only among those starting with a pro-nociceptive pattern. This change was found to be associated with the degree of pain alleviation. Thus, the notion of plasticity of the pain inhibitory capabilities is supported by the results, although it does not apply to all patients. The question of whether the change in CPM is a consequence of the specific mechanism of pain alleviation by the drug used in this study, or a mere consequence of pain alleviation, cannot be answered here, as only 1 analgesic agent was used. A hint towards the reversal of pro-nociceptivity by mechanism-independent pain alleviation is provided by the improvement in mTS in response to duloxetine. This agent is expected, at least theoretically, to alleviate pain through a mechanism different from the sensitization expressed by the enhanced mTS.

The results of this study call for the clinical application of the CPM as a screening tool before treatment selection. There are, however, several difficulties in making this CPM protocol a usable bedside test. Our current protocol requires relatively long noxious stimuli, which could be undesirable to some of the patients. Furthermore, we use both a temperature-controlled water bath and a thermal stimulator, representing an expensive and somewhat cumbersome setup. Obviously, this protocol should be simplified to routinely apply it in the clinical setting. To determine the validity of a modified protocol, one needs to show that it is at least as good as the former procedure used in the relevant clinical setup. To this end, our findings suggest the relevance of a substantial shortening of the test stimulus, as a CPM calculation based on either the first or the second pain scores obtained with the 'test stimulus' was found to provide similar information to that of the mean CPM calculated by averaging all 3 pain scores. Although this is a small step toward shortening and simplifying the protocol, additional research may identify other steps, such as the use of conditioning stimuli other than water immersion or a reduction in stimuli intensity.

The finding that patients with higher sensory thresholds, that is, a higher severity of neuropathy, demonstrated more efficient CPM is counter-intuitive, as one would expect CPM to become less efficient as the disease progresses. A possible explanation could relate to the fact that diabetic neuropathy pain does not directly correspond to the extent of neurological deficit. Although the latter typically worsens as the disease progresses, pain can be higher during periods of metabolic imbalance and tends to decrease and even disappear in the very long-term neuropathies, where substantial neuro-deficit is found. In phases with high pain activity, CPM may be rendered less efficient, being 'consumed' by the inhibitory efforts of the CNS due to the clinical pain. In turn, during late non-painful stages, CPM can fully recover.

The lack of correlation between the neuropathic pain intensity and CPM efficiency is intriguing. The fact that pain intensity did not predict drug efficacy, whereas CPM efficiency did, suggests that CPM represents a distinct and independent facet of the nociceptive profile. This parameter, which had already been shown to be relevant in pain prediction, also emerges here as a prominent trait of the pain modulation mechanism. However, the observed change in CPM efficiency in response to treatment suggests that it encompasses state features as well. This complex character must be taken into consideration when examining CPM in clinical studies.

The conclusions of the current work are limited by several factors. First, our design was that of an exploratory study rather than a 'classical' parallel randomized double-blind trial, which could have provided a more solid proof of concept to our hypothesis. Second, duration of the placebo phase was shorter than that of the drug, a factor that could have minimized the effect of the placebo. Third, the size of the study population was relatively small. We hope that this study will inspire further research along the lines of pain modulation–based prediction of treatment efficacy in neuropathic and other pains.

4.1. Conclusion

In summary, the findings of this study provide an initial indication that a short and simple CPM test can help to identify which patients are likely or unlikely to benefit from SNRIs, thereby constituting a step toward personalized therapy in pain medicine. As such, the psychophysical testing of pain modulation seems to be able to provide useful information for drug selection in neuropathic pain patients, thus carrying the potential for shortening the long and painful trial-and-error process of finding the appropriate medication for each individual patient.

Conflict of interest statement

No authors report having any potential conflict of interest with this study.

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