

Original article

Tapentadol effects on brain response to pain in sensitized patients with knee osteoarthritis

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Abstract

Objective. Pain sensitization, in the form of knee tenderness and anatomically spread hyperalgesia, is notably common in patients with knee OA and is often refractory to conventional interventions. Tapentadol, as an opioid receptor agonist and noradrenaline reuptake inhibitor, has been proposed as a potentially effective symptomatic treatment for pain-sensitized OA patients. We empirically tested whether tapentadol could attenuate brain response to painful stimulation on the tender knee using functional MRI.

Methods. Painful pressure stimulation was applied to the articular interline and the tibial surface, a commonly sensitized site surrounding the joint. Thirty patients completed the crossover trial designed to compare prolonged release tapentadol and placebo effects administered over 14 days.

Results. We found no effects in the direction of the prediction. Instead, patients administered with tapentadol showed stronger activation in response to pressure on the tender site in the right prefrontal cortex and somatosensory cortices. The somatosensory effect was compatible with the spread of neural activation around the knee cortical representation. Consistent with the functional MRI findings, the patients showed higher clinical ratings of pain sensitization under tapentadol and a significant positive association was identified between the number of tapentadol tablets and the evoked subjective pain.

Conclusion. The tapentadol effect paradoxically involved both the spread of the somatosensory cortex response and a stronger activation in prefrontal areas with a recognized role in the appraisal of pain sensations. Further studies are warranted to explore how OA patients may benefit from powerful analgesic drugs without the associated risks of prolonged use.

Trial registration. EudraCT, <https://eudract.ema.europa.eu>, 2016–005082–31.

Key words: osteoarthritis, functional MRI, brain activation, pain sensitization, opioids, sensory cortex

Rheumatology key messages

- The study presents data on opioid-related pain sensitization in patients with osteoarthritis.
- We found stronger brain activation in response to pressure on the knee tender site.
- This functional MRI study illustrates how opioids may paradoxically sensitize patients to pain.

Introduction

Refractory, disabling pain is frequently associated with CNS sensitization, which involves a variety of pathophysiological phenomena increasing the excitability of nociceptive pathways. Pain sensitization is manifested

as pain hypersensitivity with anatomically spread hyperalgesia and enhanced temporal summation of pain following repeated stimulation [1]. Pain sensitization is common in chronic knee OA patients [2]. In a previous study by our group [3], 55% of OA patients showed some evidence of pain sensitization, and it was considered clinically severe in 32% of OA patients.

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In this context, the potential clinical benefits of drugs capable of targeting these levels of nociceptive processing are well worth exploring. Tapentadol, as a μ -opioid receptor agonist and noradrenaline reuptake inhibitor, a priori, is a privileged treatment agent for pain central sensitization, because it may interfere with the transmission and processing of nociceptive information at various points in the CNS; it would also activate the descending inhibitory projections at the supraspinal level [4–6]. However, a paradoxically opposite effect of pain sensitization has been described for the use of drugs with opioid action [7, 8]. Therefore, the suitability of tapentadol for the prolonged treatment of pain-sensitized OA patients should optimally be tested in an empirical manner.

A limitation in testing treatments is partly related to the inherent subjectivity and variability of pain ratings. Consequently, there is significant interest in developing objective measures of the analgesic effect. One potential option is the use of brain imaging techniques such as functional MRI (fMRI), which may comprehensively assess neural activity related to the variety of dimensions associated with the pain experience [3, 9–11].

We have used fMRI to specifically assess the effects of tapentadol on brain response to painful stimulation in knee OA patients with clinical evidence of pain sensitization. Pressure stimuli were separately applied to the painful knee at the articular interline (test 1) and at the superior tibial surface, a commonly sensitized site surrounding the joint (test 2). Our primary objective was to compare placebo and tapentadol effects on pain-evoked brain activity (primary outcome measure). We hypothesized that tapentadol would attenuate such a brain response compared with placebo. In addition, based on the opportunity of characterizing a diversity of pain dimensions, we explored whether the imaging approach could contribute to elucidating potential action mechanisms of the hypothesized effects on pain sensitization.

Methods

Overview of study design

The study was a double-blind, randomized, placebo-controlled, three-phase crossover trial. After a screening visit, patients participated in three treatment conditions: tapentadol, placebo and no treatment, at the end of which an fMRI exam was administered in each case. The rationale for including a non-treatment condition was to enable estimation of the placebo effect as a reference. The duration of each treatment phase was 14 days, and the time between treatments was 14–21 days. The order of the treatment phases was randomized. Independent pharmacists dispensed the compounds to the investigator according to a randomization list, while the investigators and the patients were constantly kept blind to the treatment assignment.

Study population

Participants were recruited by rheumatology researchers from a referral OA Unit at the Hospital del Mar, Barcelona, in 2019 and 2020. The study was conducted in accordance with the principles expressed in the Declaration of Helsinki and was approved by the Ethical Committee of Clinical Research of the Parc de Salut Mar, Barcelona (ref. MP-TAP-2016–01) and the Spanish Agency of Medicine and Sanitary Products (ref. MUH/CLIN/EC). All patients provided written informed consent. The trial was designed according to CONSORT recommendations [12] and was registered in the EudraCT (European Union Drug Regulating Authorities Clinical Trials) database, identifier number 2016–005082–31, title: *Assessment of tapentadol effects on patients with pain central sensitization using functional MRI*.

Eligibility criteria

A patient was eligible for inclusion if the following criteria applied: (i) Radiological and clinical diagnosis of knee OA based upon American College of Rheumatology [13] criteria, (ii) Pain sensitization affecting the knee defined by combining clinical and experimental (pain thresholds) evidence, (iii) Patients with Brief Pain Inventory [14] item 5 score of 6–10 points at screening and (iv) Subjects either male or female and at least 45 years of age who could be treated in accordance with the technical specifications of summary of product characteristics (SmPC).

Patients were not eligible if they were female with childbearing potential, showed body weight >120 kg (a restriction for MRI), had severe or non-stable medical conditions, or showed prior intolerance to opioids. Treatments not allowed were analgesic and anti-inflammatory drugs (within the previous 3 days), injections in the joint or muscle (within the previous 3 months), tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors (as a recent, <6 weeks, prescription) and monoamine oxidase inhibitors. Subjects were not permitted to exercise heavily for 12 h prior to fMRI assessment.

Rescue medication (paracetamol 1 g/8 h) was allowed, but was withdrawn for a minimum of 24 h prior to the fMRI assessment. Subjects could take their chronic (non-analgesic and non-anti-inflammatory) medication if the treatments had been followed continuously for at least 6 weeks prior to assessment.

Drug dosage

Patients received a tailored oral dose of prolonged-release tapentadol hydrochloride for 14 consecutive days before the fMRI session, or placebo with an identical regime and appearance before the corresponding fMRI session. Flexible dose tailoring (titration) started with an evening dose of 50 mg, which was increased in successive steps up to 250 mg a day if tolerability was good (Supplementary Table S1, available at *Rheumatology* online).

Randomization

Patients were assigned to one of the six possible treatment sequences in accordance with a randomization schedule (A/B/C; A/C/B; B/A/C; B/C/A; C/A/B; C/B/A. A: tapentadol, B: placebo, C: no treatment) with an equal allocation ratio (1:1:1:1:1:1). The randomization scheme was generated through the website Randomization.com (<http://www.randomization.com>) using the second generator, which creates random permutations of treatments for situations in which subjects receive all the treatments in random order. The system generated a unique number for each randomized patient, and the randomization schedule was stratified in blocks of 12. A single independent researcher was aware of the randomization information (L.B.H.).

Sample size

There is no consensus as to sample size estimation for fMRI studies. Empirical experiments have demonstrated that a number above 24 subjects is optimal to achieve 80% power for a threshold of 0.05 in conventional task activation experiments [15].

Clinical assessments

Screening assessments included complete medical history, physical examination, ECG, X-ray of the knee and an inclusion/exclusion criteria checklist. At screening, the knee, right or left, to be stimulated during fMRI was selected based on the most symptomatic side. Potential candidates were fully briefed on the study. If they agreed to participate, they duly signed the informed consent and were assigned a unique study number.

Patients were clinically and experimentally evaluated on the last day of each treatment phase prior to the fMRI session, which always took place in the afternoon, following the final morning dose. The severity of pain sensitization was evaluated by means of a Pain Sensitization Global Score combining the ratings of (i) clinical pain intensity, (ii) clinical pain spreading, (iii) number of tender points and (iv) pain temporal summation. To compute such a Pain Sensitization Global Score, the values of the four ratings, each scaled to 0–10 points, were added to provide a single score ranging from 0 to 40.

Clinical pain intensity

The assessment of clinical pain intensity was based on items 3–6 of the Brief Pain Inventory [14], which rate mechanical pain (mean, maximum and minimum) in the preceding 24 h and current pain using 11-point numerical rating scales (NRSs) (ranging from 0, no pain, to 10, the most severe pain). There are four ratings in total, so there is a maximum score of 40.

Pain spreading

Pain spreading was clinically evaluated by manual palpation of the knee and surrounding areas. A highly trained experimenter (G.M.V.) rated the severity of pain verbally and non-verbally expressed by the patient as mild (score 2), moderate (score 4) and severe (score 6).

Severe pain was given a score of 5 if it did not exceed half of the area examined, a score of 3 similarly for non-extensive moderate pain and a score of 1 for non-extensive mild pain.

Number of tender points

The number of tender points was experimentally determined. A custom-made MRI compatible pressure algometer (see [Supplementary Data S1](#), available at *Rheumatology* online) was used [3] to measure *pressure pain thresholds*. The probe (1cm²) was placed perpendicular to the selected anatomical sites, and pressure was applied (30 kPa/s) until the participant defined the pressure as pain. Pressure pain thresholds were measured twice on each site of the extended Arendt-Nielsen peripatellar map [3, 16, 17] ([Supplementary Fig. S1](#), available at *Rheumatology* online), and the mean of both measures was used.

Temporal summation

Temporal summation to repeated painful pressure stimulation was assessed on the anterior/medial tibial surface, which was one of the sites to be stimulated during fMRI. The sequential stimulation consisted of 10 pressure stimuli (1 s duration and 1 s interval) applied with the algometer at the pressure pain threshold level [16]. The subjects rated pain intensity for the first and last stimuli with an 11-point NRS.

Additional clinical assessments

Additional clinical assessments to characterize the patient sample included: the WOMAC physical-function scale [18], the PainDETECT questionnaire [19], and the Hospital Anxiety and Depression Scale (HADS) [20, 21]. An 11-point pain rating was generated using a pressure of 4 kg/cm² over 2 s on the tibial surface, as an estimation of regional pain sensitization. An 11-point rating of spontaneous, resting subjective pain perceived in the whole body was used as a measure of primary, FM-like pain sensitization. No patient was included with a history or previous medical diagnosis of FM, and no patient showed evidence of global sensitization according to the rating of spontaneous body pain and pain extension in the body diagram in item 2 of the Brief Pain Inventory [14].

Functional MRI testing stimuli

Test 1 involved pressure stimulation on the medial articular interline of the selected kneel, and test 2 involved pressure stimulation on the anterior surface of the tibial region. A complete description of the adopted procedures is reported in [Supplementary Data S1](#) and [Supplementary Fig. S2](#), available at *Rheumatology* online.

Functional MRI

Details of fMRI acquisition, preprocessing and the control of potential head motion effects are provided in [Supplementary Material](#). The study included two fMRI

sequences; the Knee Articular Interline test and the Tibial Surface test, with an identical block paradigm alternating 11 baseline periods of 20 s (plus a final baseline period of 30 s) with 11 painful stimulation periods of 10 s (total 6 min) (Supplementary Fig. S2, available at *Rheumatology* online).

Functional MRI analysis

First-level (single-subject) analysis

The fMRI signal response at each voxel was modelled using study-specific regressors adjusted to the actual brain response to our pressure stimulation. In previous studies of independent samples using similar stimuli, temporal analyses demonstrated that blocks of 10 s of pressure stimulation generating pain of moderate (5–7/10) intensity evoke a brain response lasting about 16 s [3, 10, 22]. Subjective pain was perceived with a duration similar to brain activation [22]. Therefore, we modelled brain activation with a boxcar regressor considering 11 activation blocks of 16 s and applying a hemodynamic delay of 4 s (Supplementary Fig. S2, available at *Rheumatology* online). Brain activation (the primary outcome measure) was estimated based on the statistical parametric mapping (SPM) contrast 'resting blocks < pressure blocks'.

Group-level analysis

The resulting first-level SPM contrast images were carried forward to group-level analyses. Paired *t*-tests were used to compare brain activity evoked during tapentadol and placebo conditions (primary analysis), including data from 30 patients in the interline analysis and 29 patients in the tibial analysis. In addition, each intervention was compared with the no-treatment condition. One-sample *t*-test designs were used to generate group activation maps. In this case, the groups included an identical number of subjects (i.e. patients with data from the three conditions) to make the maps comparable upon visual inspection ($n=29$ for the interline test and $n=27$ for the tibial test). In addition, voxel-wise linear regression was used to test the association between the number of tablets taken and evoked brain activity.

As the hemisphere (right or left) activated at the primary and second somatosensory cortices depends on the body side (left or right) stimulated, a subanalysis was conducted using right-to-left flipped images for the 14 patients stimulated on their left knee and original (non-flipped) images for the 16 patients stimulated on their right knee.

In all analyses, results were considered significant when clusters formed at a threshold of $P<0.005$ survived whole-brain family-wise error (FWE) correction ($P<0.05$), calculated by means of SPM. SPM-set level-corrected whole-brain results were also considered to provide a more complete characterization of changes at the pain network level. The statistical analysis of the

behavioural data involved paired *t*-tests and Pearson's correlations.

Results

Thirty patients were finally deemed valid for the primary study analysis involving the assessment of tapentadol treatment effects compared with placebo. Fig. 1 details the participant selection flow diagram. Table 1 reports the clinical characteristics of the sample. The final dose (on the last day) of tapentadol was 250 mg a day (step 4) in all but three patients.

Intervention effects on subjective pain sensitization measures

We were unable to demonstrate a positive, relieving effect of tapentadol. Instead, patients under the placebo condition showed a significantly higher reduction in pain sensitization compared with tapentadol. The Pain Sensitization Global Score showed a mean (s.d.) of 16.5 (6.1) points under tapentadol treatment and 14.0 (6.4) under placebo ($t=3.0$ and $P=0.006$). Table 2 summarizes the results of the pain sensitization measure analysis and Supplementary Table S2 (available at *Rheumatology* online) the analysis of general pain-related indices.

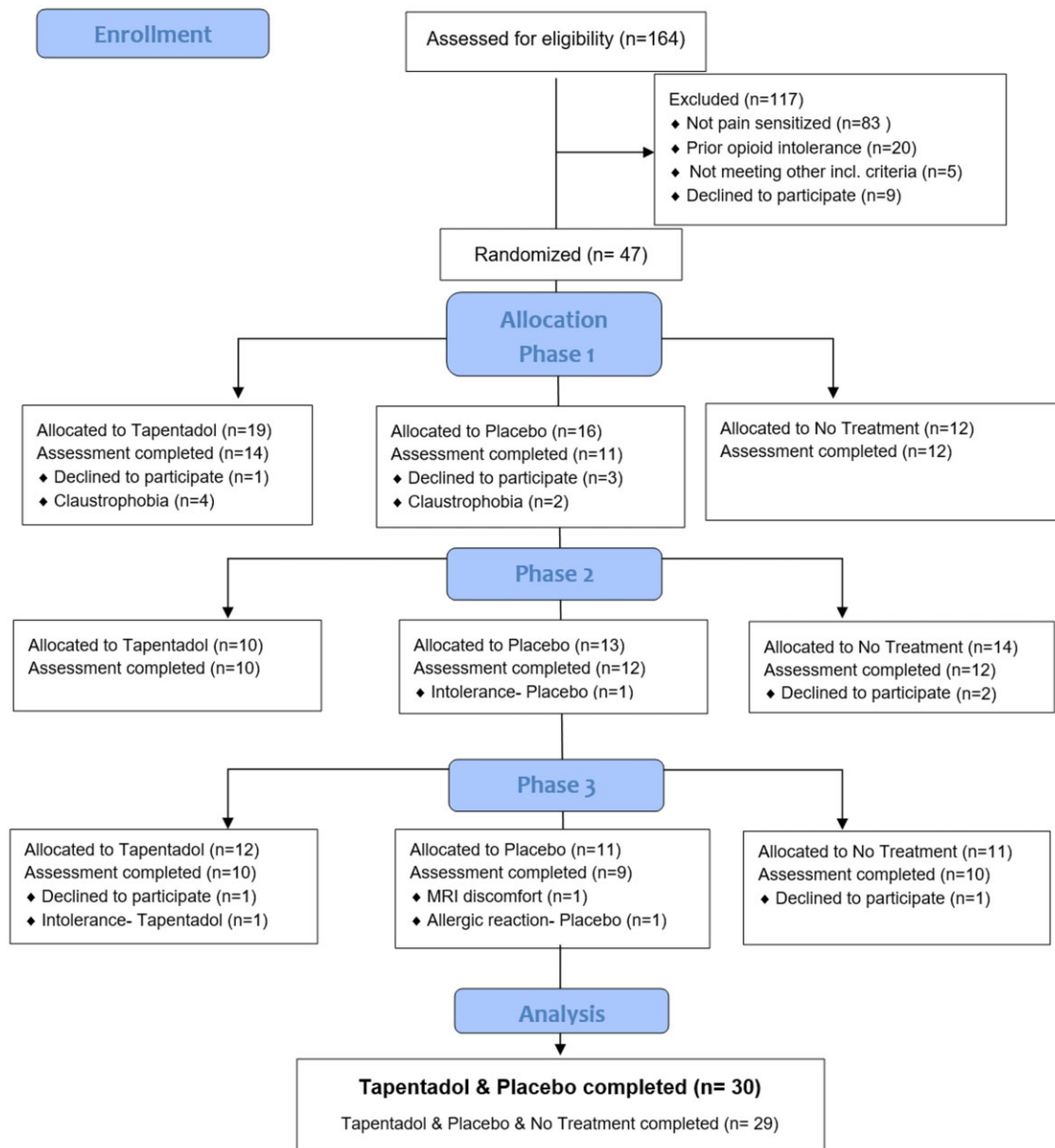
Intervention effects on subjective pain evoked during fMRI testing

Similarly, tapentadol did not attenuate pain generated by knee interline and tibial surface stimulation during the fMRI experiments (Supplementary Table S3, available at *Rheumatology* online). In contrast, a significant association ($r=0.54$; $P=0.002$) was observed between the number of tapentadol tablets taken during the whole treatment period and subjective pain perceived when applying pressure on the tibial surface (Supplementary Fig. S3, available at *Rheumatology* online). A subanalysis excluding the patients who took a low dose (20 tablets or less) indicates that the association tended to involve other sensitization measures (Supplementary Table S4, available at *Rheumatology* online). The number of placebo tablets did not correlate with any measure of pain.

Functional MRI results

Knee articular interline test

Fig. 2 shows 3D brain images illustrating one-sample *t*-tests results for the three study conditions, and Supplementary Fig. S4 (available at *Rheumatology* online) shows representative orthogonal views. There was no apparent reduction in brain activation during knee interline stimulation under tapentadol treatment compared with placebo. Paired comparisons showed only one significant effect in the knee articular interline analysis. Significant neural activation reduction was identified under placebo compared with no treatment, in the paracentral lobule involving the somatosensory area in

Fig. 1 Participant flow diagram

the cortical representation of the lower limb (Supplementary Fig. S5 and Supplementary Table S5, available at *Rheumatology* online).

Tibial surface test

Fig. 3 similarly presents 3D images to illustrate one-sample *t*-test results for this analysis (see also Supplementary Fig. S4, available at *Rheumatology* online). There was an apparent enhancement of brain activation during tibial surface stimulation under tapentadol treatment compared with the other conditions upon visual inspection. Paired *t*-tests confirmed significant effects in this analysis in the form of stronger activation

under tapentadol compared with placebo in the paracentral lobule and right dorsal prefrontal cortex (Fig. 4 and Supplementary Table S5, available at *Rheumatology* online). No association was found between the number of tapentadol tablets and brain activation.

A subanalysis was conducted using flipped images in patients with affected left knees (and non-flipped images for right knee cases) to evaluate the lateralized effects in the somatosensory cortices and closely related regions (motor and supplementary areas). Supplementary Fig. S6, available at *Rheumatology* online, illustrates one-sample *t*-test results for patients with complete tibial test data for the three conditions. This analysis showed

the most demonstrative results of tapentadol's effects on the sensory areas. Fig. 5 illustrates the results obtained by comparing tapentadol and placebo conditions in the flipped subanalysis. Significantly higher activation was identified under tapentadol in the primary somatosensory cortex ipsilateral (and not contralateral) to the stimulated knee (Supplementary Table S5, available at *Rheumatology* online). A similar effect was also identified in the ipsilateral second somatosensory area (parietal operculum), paracentral lobule, superior parietal cortex and premotor cortex. Such an anatomical pattern expresses a cortical spreading of neural activation, which is consistent with the observed spreading of painful, tender areas around the knee.

Fig. 5 additionally shows the activation reduction effect of placebo compared with no treatment in the articular interline test analysis using flipped images. In this case, significant differences were identified

in the paracentral lobule, with a lateralized effect extending to the somatosensory cortex contralateral to the stimulated knee (Supplementary Table S5, available at *Rheumatology* online). Contralateral activations are expected due to sensory pathway decussation.

A further analysis revealed that the cortical activation spreading by tapentadol may in part express reduced neural inhibition. Indeed, Supplementary Fig. S7 (available at *Rheumatology* online) shows group one-sample results for the contrast 'activation condition (pressure on) < resting condition (pressure off)' at a low threshold ($P < 0.05$), which identifies neural areas inhibited during painful stimulation in the tibial test analysis using flipped images. The model shows that inhibited areas in the placebo condition involved the ipsilateral (and not the contralateral) primary somatosensory cortex and surrounding ipsilateral and contralateral cortices. Such a pattern of neural inhibition was not evident in the tapentadol condition map.

TABLE 1 Clinical characteristics of the study sample ($n = 30$)

Age, years	63.4 (9.1)
Sex, number F/M	23/7
Radiological severity	2.3 (0.5)
WOMAC Index, total	40.4 (20.1)
PainDetect (max. 38 points)	10.4 (6.0)
Tibial region pain (regional sensitization) ^{ab}	5.8 (2.3)
Spontaneous body pain (global sensitization) [#]	0.4 (1.4)
HADS Anxiety score (max. 21 points)	7.1 (6.1)
HADS Depression score (max. 21 points)	5.8 (4.9)
Tapentadol number of tablets	34 (9.1)
Placebo number of tablets	35 (7.2)

Data are expressed as mean (s.d.). ^aPain generated with a pressure of 4 kg/cm² during 2 s. ^bRated using an 11-point numerical rating scale. HADS, Hospital Anxiety and Depression Scale.

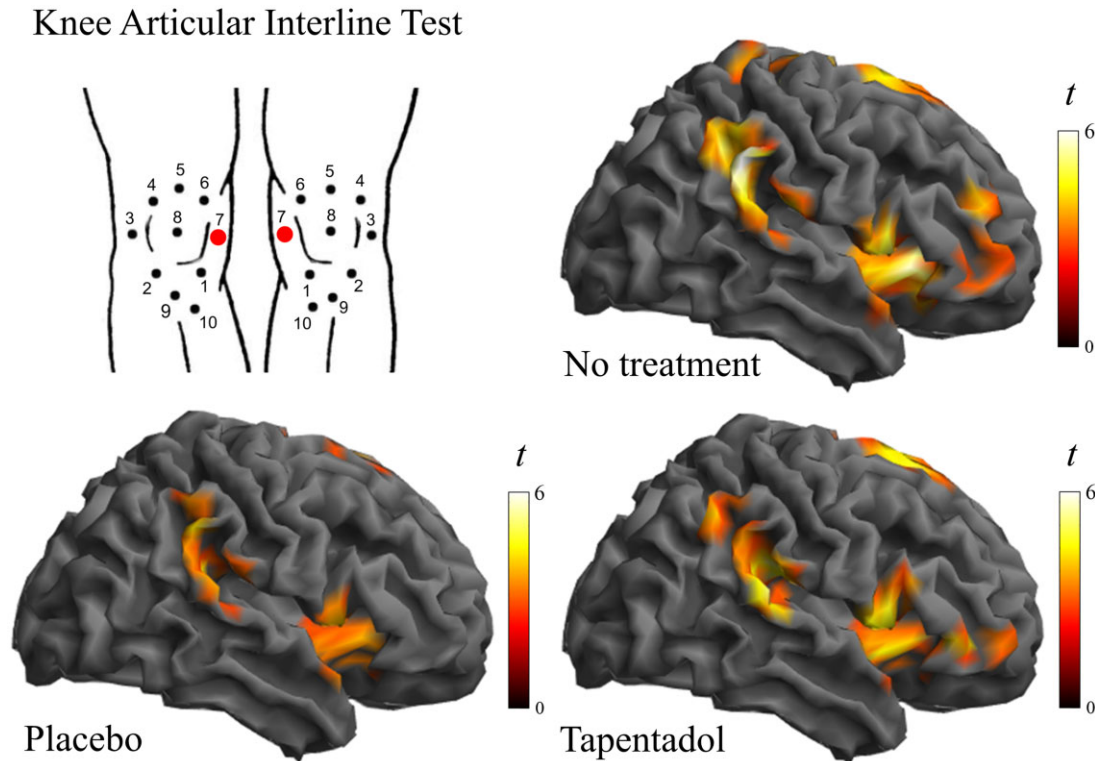
TABLE 2 Pain sensitization measures

	Tapentadol ($n = 30$), mean (s.d.)	Placebo ($n = 30$), mean (s.d.)	No treat. ($n = 29$) mean (s.d.)	Tapentadol vs Placebo (df = 29)	Tapentadol vs No Treat. (df = 28)	Placebo vs No treat. (df = 28)
Pain sensitization global score	16.5 (6.1)	14.0 (6.4)	17.5 (5.0)	$t = 3.0$ $P = 0.006$	$t = -1.1$ $P = 0.278$	$t = -4.5$ $P = 0.0001$
Clinical pain intensity (BPI)	17.8 (7.0)	15.4 (7.6)	19.0 (6.9)	$t = 1.6$ $P = 0.128$	$t = -0.7$ $P = 0.521$	$t = -2.3$ $P = 0.026$
Clinical pain spreading	1.4 (0.9)	1.0 (0.7)	1.3 (0.8)	$t = 2.8$, $P = 0.008$	$t = 0.5$, $P = 0.636$	$t = -2.3$, $P = 0.027$
Number of tender points	5.8 (2.7)	5.3 (2.5)	6.7 (2.4)	$t = 1.3$, $P = 0.196$	$t = -2.5$, $P = 0.018$	$t = -3.6$, $P = 0.001$
Pain temporal summation	1.7 (1.7)	1.4 (2.0)	1.7 (2.1)	$t = 0.7$, $P = 0.474$	$t = 0.1$, $P = 0.960$	$t = -0.8$, $P = 0.426$

BPI: Brief Pain Inventory, items 3–6, maximum score 40. No treat: no-treatment condition.

Discussion

We have empirically tested whether a treatment agent with dual opioid and noradrenergic action such as tapentadol could attenuate the brain response to pain in sensitized patients with knee OA. We found no effect in the direction of the prediction. Instead, patients under tapentadol showed stronger activation in response to knee painful stimulation in the right prefrontal cortex and somatosensory cortices compared with placebo. The effect was more evident when applying pressure stimuli on the tibial surface, which more accurately represents the sensitized component of knee pain. A significant positive association was identified between the number of tapentadol tablets taken and subjective pain evoked during tibial surface stimulation. The fMRI findings were consistent with the drug's clinical effect, specifically on measures of pain sensitization showing a significant

Fig. 2 3D views showing one-sample *t* test results from the knee articular interline test analysis

increase in severity under tapentadol. fMRI allows us to identify neural activity related to different aspects of the composite pain experience from the primary sensory processing to the ultimate individual appraisal of the perceived sensation [23]. We found tapentadol-related effects at both extremes of the brain's response to pain. Indeed, significant changes involved the right prefrontal lobe, which deals with the highest-order processing of noxious stimuli by coding stimulus intensity, unpleasantness and potential danger [22, 24], and the somatosensory cortices that contribute to pain experience by coding the body site and sensory quality of the stimulus [25].

The results at the sensory level indicate that the tapentadol effect may be related to the cortical spreading of neural changes around the cortical representation of the knee. That is, instead of reduced activity in the knee's primary cortex associated with the placebo effect, tapentadol was associated with stronger activation in primary and second somatosensory areas ipsilateral to the stimulated knee and sensorimotor areas surrounding its cortical representation. Such spatial spreading of the cortical sensory response to pressure stimulation is consistent with the observed spread of painful, tender areas around the knee. The analysis of brain deactivations suggests that reduced inhibition may contribute to the augmented cortical response.

Our results further expose a paradox in medicine implying that the most powerful analgesic drugs may

ultimately sensitize the nociceptive system and exacerbate pain instead [7, 8]. The phenomenon has been described in association with prolonged opioid use [8], but also with high doses of short-acting opioids [7]. The main mechanism involved in opioid-related pain sensitization includes synaptic adaptations within the descending analgesic system and the activation of inflammation-related pain mediators at the neuroimmune interface [8]. Based on the combination of μ -opioid receptor affinity and noradrenaline reuptake inhibitory action on the descending analgesic system [26], tapentadol was thus proposed as a potential candidate for treating pain-sensitized patients [4–6, 27]. However, the results from our empirical testing suggest that repeated tapentadol doses in sensitized knee OA patients may also paradoxically exacerbate pain and the evoked brain response. It would also be of interest to evaluate by neuroimaging the effects of μ -opioid receptor agonists and noradrenaline reuptake inhibitors separately.

In the context of the study limitations, it is important to note that the results cannot currently be generalized to other clinical situations, such as pain of neuropathic origin, non-sensitized OA patients, other OA pain locations, or different drug dosages. For instance, the duration of treatment in our study was 14 days, and the maximum dose achieved was 250 mg a day, whereas, in a recent study by van de Donk *et al.* [28], higher doses of tapentadol for 3 months significantly reduced

Fig. 3 3D views showing one-sample *t* test results from the tibial surface test analysis

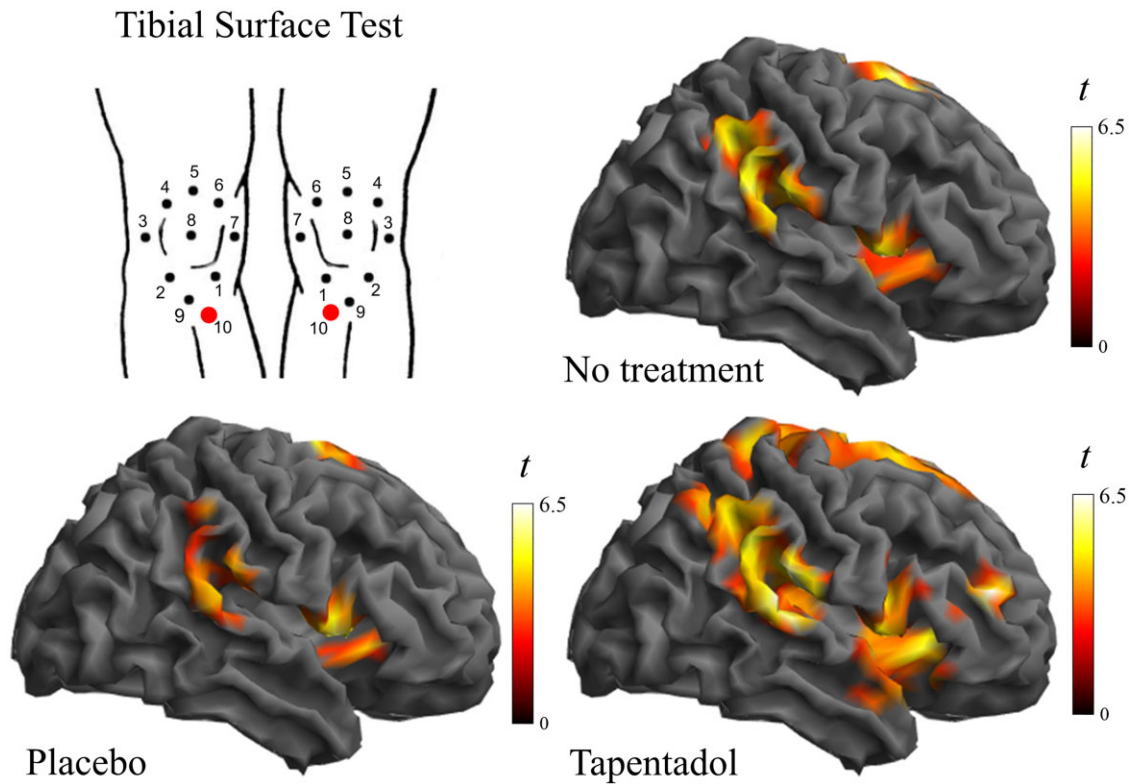


Fig. 4 Areas showing stronger activation under tapentadol compared with placebo during tibial surface stimulation

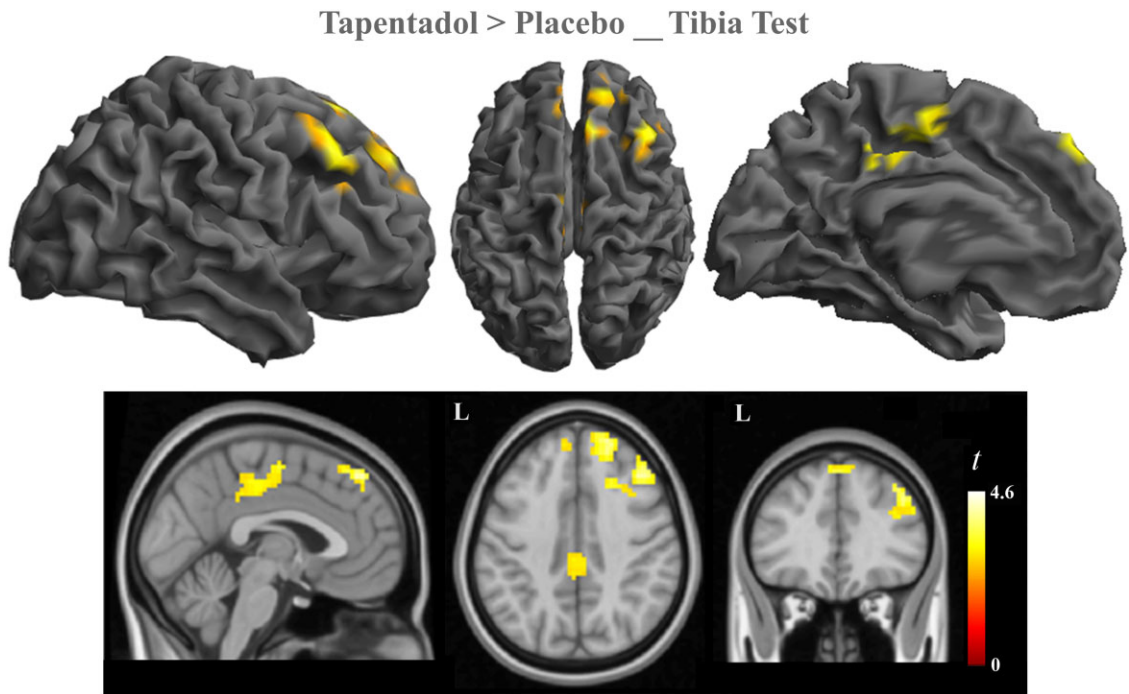
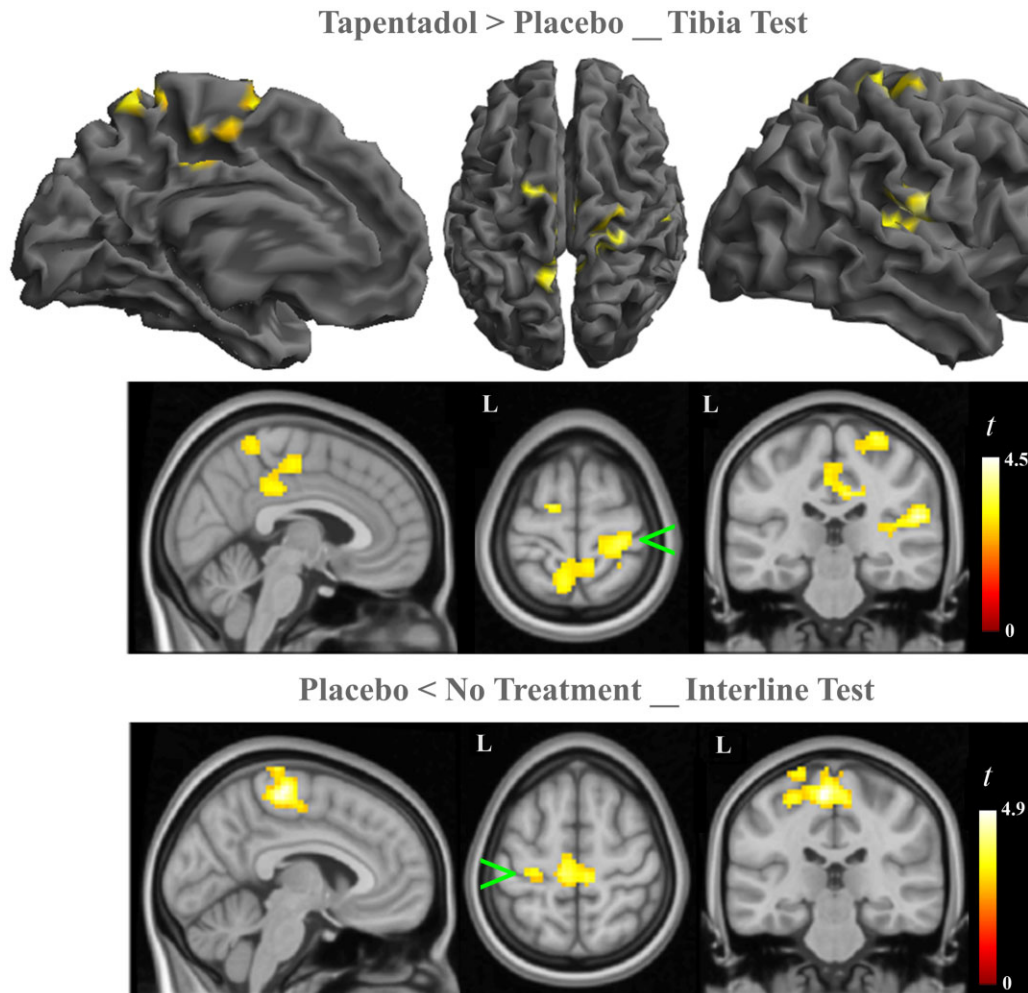


Fig. 5 Effects on brain activation identified in the analysis of flipped images

Top views show areas with stronger activation under tapentadol compared with placebo during tibial surface stimulation. The arrowhead indicates the somatosensory cortex ipsilateral to the stimulated knee. Bottom views show areas with activation reduction under placebo compared with no treatment in the articular interline test. The arrowhead indicates the somatosensory cortex contralateral to the stimulated knee.

spontaneous pain and temporal summation in a subgroup of chronic low back pain patients with defective central pain inhibition. We aimed at specifically assessing the acute effect of the drug on the brain, as opposed to determining its usefulness as a chronic treatment, to locate brain structures potentially sensitive to tapentadol. The strong placebo effects on chronic pain may certainly reduce trial sensitivity, particularly in short treatment regimens [29, 30]. However, in our study, the effects went in the opposite direction with the *active drug* showing significantly less attenuation of brain response to painful stimulation than the placebo.

Although the present study was based on a number of fMRI assessments deemed adequate to answer the research question, the sample size was limited, for instance, in terms of distinguishing the effects of sex on

pain sensitization. This is a relevant issue, because there are data indicating that opioid-related pain sensitization may be more severe in males [7]. A higher number of assessed patients may also have made it possible to evaluate lateralized brain changes depending on the stimulated knee, right or left, with no need to flip the images for the analysis.

In conclusion, the current clinical trial was unable to demonstrate attenuated brain response to painful knee stimulation in sensitized knee OA patients treated with tapentadol. Instead, the tapentadol effect was paradoxically associated with both spreading the sensory component of the cortical response and stronger activation of prefrontal cortex areas with a recognized role in the appraisal of the pain sensation. Further studies are warranted to explore how OA patients may benefit from

powerful analgesic drugs without the associated risks of prolonged use.

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Disclosure statement: The authors have declared no conflicts of interest.

Data availability statement

The data is available upon request to interested qualified researchers. Data requests should be sent to the Corresponding Author, who can be contacted via 21404jpn@comb.cat.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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