

Tapentadol potentiates descending pain inhibition in chronic pain patients with diabetic polyneuropathy

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Editor's key points

- Tapentadol is a μ -opioid agonist and also inhibits norepinephrine reuptake.
- This study evaluates the main analgesic mechanisms of tapentadol in diabetic neuropathy.
- Conditioned pain modulation and offset analgesia were used to investigate the endogenous pain pathways.
- Tapentadol's analgesic effect in diabetic neuropathy is mainly via activation of descending inhibitory pathways.

Background. Tapentadol is an analgesic agent for treatment of acute and chronic pain that activates the μ -opioid receptor combined with inhibition of neuronal norepinephrine reuptake. Both mechanisms are implicated in activation of descending inhibitory pain pathways. In this study, we investigated the influence of tapentadol on conditioned pain modulation (CPM, an experimental measure of endogenous pain inhibition that gates incoming pain signals as a consequence of a preceding tonic painful stimulus) and offset analgesia (OA, a test in which a disproportionately large amount of analgesia becomes apparent upon a slight decrease in noxious heat stimulation).

Methods. Twenty-four patients with diabetic polyneuropathy (DPN) were randomized to receive daily treatment with tapentadol sustained-release (SR) [average daily dose 433 (31) mg] or placebo for 4 weeks. CPM and OA were measured before and on the last day of treatment.

Results. Before treatment, none of the patients had significant CPM or OA responses. At week 4 of treatment, CPM was significantly activated by tapentadol SR and coincided with significant analgesic responses. CPM increased from 9.1 (5.4)% (baseline) to 14.3 (7.2)% (placebo) and 24.2 (7.7)% (tapentadol SR, $P < 0.001$ vs placebo); relief of DPN pain was also greater in patients treated with tapentadol than placebo ($P = 0.028$). Neither placebo nor tapentadol SR treatment had an effect on the magnitude of the OA responses ($P = 0.78$).

Conclusions. Tapentadol's analgesic effect in chronic pain patients with DPN is dependent on activation of descending inhibitory pain pathways as observed by CPM responses.

Clinical trial registration. The study was registered at trialregister.nl under number NTR2716.

Keywords: chronic pain, diabetic polyneuropathy; conditioned pain modulation; morphine; neuropathic pain, offset analgesia; pain, tapentadol

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Endogenous pain modulatory pathways are important regulators of human pain perception. Both inhibitory and facilitatory descending pathways, originating at higher centres, modulate the activity of nociceptive neurones at the level of the spinal dorsal horn, enhancing or inhibiting noxious signal propagation to the brain.¹ A shift in the balance between pain inhibition and facilitation has been suggested to underlie the development or maintenance of many chronic pain syndromes, such as fibromyalgia, irritable bowel syndrome, chronic pancreatitis, and neuropathic pain syndromes.^{2–5} Animal studies show that effective engagement of descending inhibition protects against chronic neuropathic pain development. Various neurotransmitter systems are involved in the descending pain pathways, including endogenous opioid peptides, norepinephrine, and serotonin. Release of endogenous opioids and norepinephrine underlie pain inhibition, whereas the serotonergic

pathway has both pain inhibitory and facilitatory properties.^{6–8} The new analgesic tapentadol is a centrally acting drug with a combined mechanism of action. Tapentadol is a μ -opioid receptor (MOR) agonist (its affinity for the MOR is 50 times less than that of morphine) and inhibits neuronal reuptake of norepinephrine.^{6,9} Both mechanisms act synergistically to produce analgesia.¹⁰ Animal studies indicate that the opioidergic component is more important in the treatment of acute pain, whereas the noradrenergic component is largely involved in the treatment of chronic neuropathic pain.⁸

As tapentadol modulates opioidergic and noradrenergic pathways simultaneously, the analgesic effect of tapentadol is thought to rely on the enhancement of descending pain inhibitory activity.¹¹ However, up to now, no studies have been conducted to confirm the presence of such an effect in humans. In the current study, the effects of tapentadol on

two experimental paradigms, conditioned pain modulation (CPM) and offset analgesia (OA), were tested in chronic pain patients with diabetic polyneuropathy (DPN). CPM is an experimental measure of endogenous pain modulation that gates incoming pain signalling as a consequence of a preceding or simultaneous tonic painful stimulation.^{12–17} OA is a test in which a disproportionately large amount of analgesia becomes apparent upon a slight decrease in noxious heat stimulation.^{18–19} Both tests have been used previously to evaluate the engagement of pain modulatory pathways.^{4, 14–19}

We performed a randomized, parallel-design, placebo-controlled study in chronic pain patients with DPN on the effect of a 4-week tapentadol treatment on CPM, OA, and pain relief. We hypothesize that tapentadol's analgesic efficacy relies, in part, on the engagement of endogenous pain inhibitory pathways.

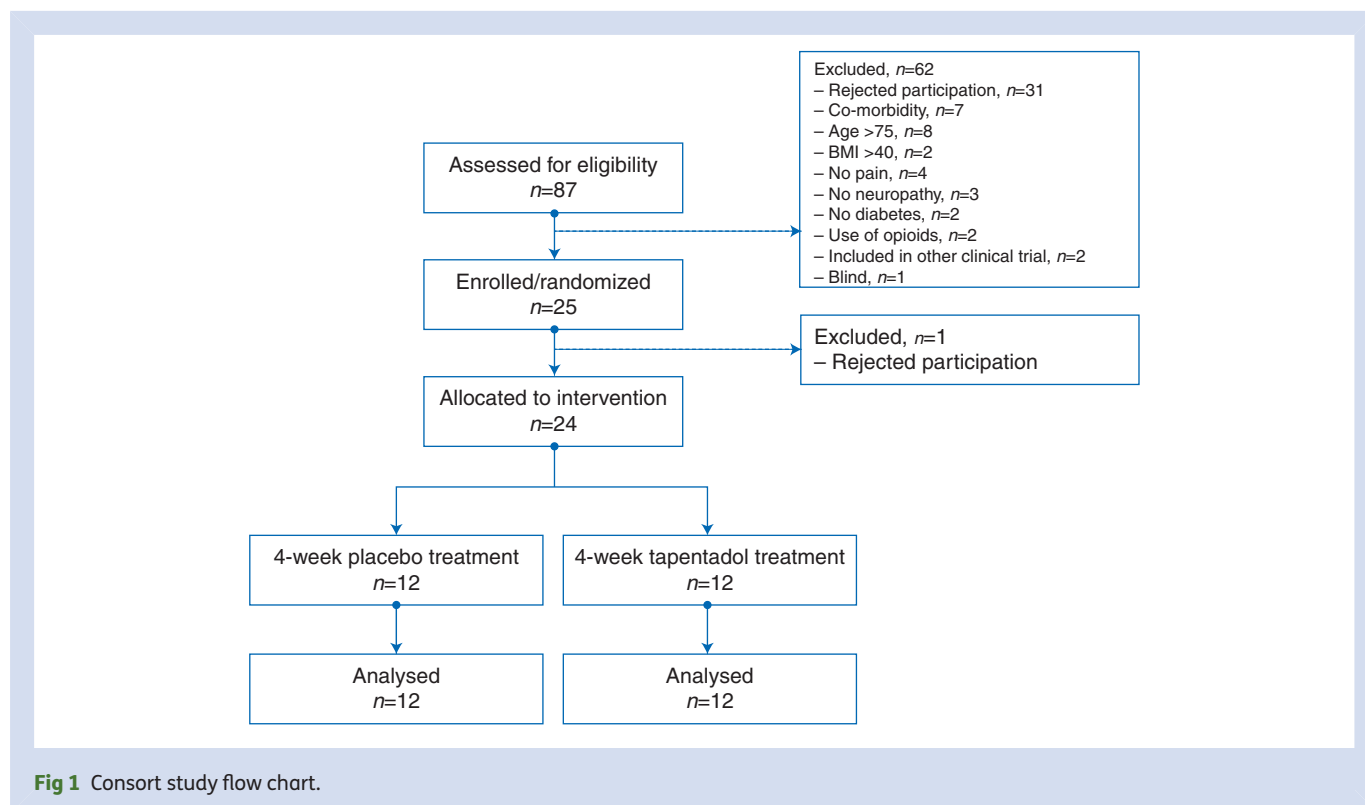
Methods

Chronic pain patients were recruited to participate in the study performed at the Leiden University Medical Center over the period January 2012–October 2012, after approval of the protocol was obtained from the local Medical Ethics Committee and the Central Committee on Research involving Human Subjects (CCMO, The Hague, The Netherlands). The study was registered at trialregister.nl under number NTR2716 and has EudraCT number 2010-012175-26. The study was registered as an addendum to an earlier trial on the effects of a single dose of tapentadol and morphine on CPM. All participants gave written informed consent and underwent a physical examination before enrolment in the study.

Patients were recruited via an advertisement in the journal of the national diabetic society. All recruited patients had diabetes and chronic pain in hands and/or legs and feet. They were included in the study when they were 18–75 yr, had a BMI below $\leq 40 \text{ kg m}^{-2}$, and had: (i) presence of at least two of the following symptoms in legs, arms, or both (in a stocking-glove distribution): (a) symmetrical dysesthesias or paresthesias, (b) burning or painful feet with nighttime worsening, or (c) peripheral tactile allodynia; and (ii) an abnormal warm or cold detection threshold, an abnormal warm or cold pain threshold, or allodynia observed with quantitative sensory testing (QST). Exclusion criteria included: indication of the presence of severe medical diseases (e.g. liver function elevation); allergy to opioids; current use of benzodiazepines and/or other sedatives; present or past use of illicit/recreational substances; present or past alcohol abuse; history of mental illness or epilepsy; pregnancy and/or lactation; current use of strong opioids; and inability to understand the purpose and instructions of the study. The patients were allowed to continue the following pain medications as long as they used a constant dose for the 8 weeks before the study and the dosage could be kept constant during the whole study period: acetaminophen, non-steroidal anti-inflammatory drugs, amitriptyline, gabapentin, and pregabalin. Patients who had been using opioids previously (and terminated treatment due to the absence of efficacy or side-effects) were eligible for inclusion.

Study design

This randomized, double-blind, placebo-controlled study was performed in 24 DPN patients (see Consort flow chart, Fig. 1).



Twelve patients were treated orally for 4 weeks with tapentadol slow release (SR), 12 others with placebo. The dose of tapentadol SR was titrated to effect starting with 100 mg twice daily in week 1, followed by 200 mg twice daily in week 2, and 250 mg twice daily in weeks 3 and 4. In the case of the presence of side-effects unacceptable to the patient, the tapentadol dose was decreased to a dose where side-effects were absent or acceptable. All patients were tested twice, once 1 day before the treatment period and once on the last day of treatment. On each study day, the subjects were familiarized with the test procedures. Next, the CPM and OA responses were obtained. Spontaneous pain scores [using an 11-point numerical rating scale (NRS) from 0 (corresponding with no pain) to 10 (corresponding with most imaginable pain)] and side-effects [presence of nausea, vomiting, drowsiness, dizziness, and dry mouth, using a dichotomous scale (yes/no)] were monitored on a weekly basis.

To get an indication of the nerve-fibre involvement in the patient population, QST was performed according to the standardized protocol of the German Research Network on Neuropathic Pain.²⁰ In short, this protocol assesses cold, heat, and mechanical detection and pain thresholds; paradoxical heat sensations; mechanical pain sensitivity; allodynia; wind-up and vibration; and pressure pain thresholds. Sensory testing was performed on the hand and foot of all pain patients included in the study.

Application of nociceptive stimuli for CPM and OA testing

Heat pain was induced on the lower part of the non-dominant arm with a 3 × 3 cm thermal probe connected to the Pathway Neurosensory Analyzer (Medoc Ltd, Ramat Yishai, Israel). The probe was calibrated according to the specifications of the manufacturer. During the heat pain stimulation, subjects continuously quantified the pain intensity level of the stimulus using a slider on a computerized potentiometer that ranged from 0 (no pain) to 100 (worst pain imaginable). This allowed for continuous monitoring of the visual analogue scale (eVAS). To overcome sensitization, the thermode was moved between different zones on the forearm and ample time was incorporated between the different heat stimuli. On each of the two study days (i.e. before treatment and at 4 weeks of treatment), the individual test temperature was determined by applying a series of heat stimuli. First, the temperature was increased from 32°C (baseline temperature) by 1.5°C s⁻¹ to a target temperature of 42°C and kept constant for 10 s. If the eVAS was <50 mm, a next test was performed increasing the target temperature in steps of 1°C. The cut-off temperature for these series was 49°C. The temperature evoking an eVAS of at least 50 mm was used during the remainder of the study.

Cold pain was induced using a cold-water reservoir produced by a rapid water-cooling system (IcyDip, IcySolutions BV, Delft, The Netherlands). The subject's foot and lower leg was immersed into the cold water reservoir, which could be set at different temperatures ranging from 6°C to 18°C. The temperature that produced an eVAS of at least 30 mm was

used in the remainder of the study. After the exposure to cold water, the subject's extremity was warmed to normal temperature using warm water collected from the counter-current outlet of the IcyDip system.

CPM and OA

The method to induce CPM has been published previously.^{2 4 14} In short, to measure CPM, two series of three pain tests were performed. One series included stimulation of the forearm with the experimental stimulus (heat pain). For this, the temperature of the heat probe gradually increased from baseline temperature (32°C) to the earlier set test temperature (at 1.5°C s⁻¹) and remained constant for 30 s. Next, the temperature rapidly returned (at 6°C s⁻¹) to baseline. The second series included stimulation with both the experimental stimulus and the conditioning stimulus (CS) (cold pain). The CS was applied 25 s before the start of the experimental stimulus and ended simultaneously with the end of the experimental stimulus. In both sessions, the subjects only rated the pain intensity level of the experimental stimulus (heat pain on the arm). There were 3 min intervals between single tests.

OA was studied by applying a three-temperature paradigm as described by Grill and Coghill.¹⁸ The temperature was ramped at 1.5°C s⁻¹ from baseline temperature to the previously set test temperature. The test temperature was kept constant for 5 s after which it was raised by 1°C for 5 s and next decreased by 1°C for 20 s. At the end of the test, the temperature quickly returned (6°C s⁻¹) to baseline. This temperature paradigm was applied three times with a 3-min interval between tests.

Randomization and blinding

Randomization and allocation was performed by the local pharmacy using a computer-generated randomization list. Placebo tablets were fabricated by the pharmacy and were identical to the tapentadol tablets in form, size, and taste. The tablets were repackaged into unmarked containers and delivered to the research team and subsequently by the research team to the patients. The research team remained blinded to treatment until all CPM and OA responses had been analysed.

Data analyses

To quantify the magnitude of CPM, the peak eVAS scores were used in the analyses. For each subject, the average peak eVAS without and with CS were calculated. Next, relative CPM responses were calculated to correct for variations in peak response between sessions and subjects using the formula:^{2 21 22} [(mean eVAS without CS stimulus - mean eVAS with CS) / (mean eVAS without CS)] × 100%.

OA responses were quantified as previously described.^{14 19} In short, the decrease in eVAS from the peak eVAS value to the eVAS nadir after the 1°C decrease in the test stimulus was measured ($\Delta eVAS$) and corrected for the value of the peak eVAS: $\Delta eVAS_C = [\Delta eVAS / (\text{peak eVAS})] \times 100\%$.

Sample size and statistical analysis

A sample size of 24 (12 per treatment level) was calculated by assuming an increase in CPM of 20% (15%) [mean (SD)] with

$\alpha=0.05$ and $\beta>0.95$. An effect of 20% was chosen as this constitutes the ‘average’ value of CPM in healthy volunteers and is probably the maximum magnitude of CPM attainable in humans.¹⁴

The effect of the CS on the relative eVAS responses was tested by two-tailed paired *t*-test. Treatment effects were assessed by two-way repeated-measures analysis of variance (factors: time and treatment). For all analyses, the software package SigmaPlot version 12.5 for Windows (Systat Software Inc., San Jose, CA, USA) was used. Data are presented as mean (SEM) unless otherwise stated and *P*-values of <0.05 were considered significant.

Table 1 Patient characteristics

| | Tapentadol | Placebo |
|---------------------------------------|-----------------|---------------|
| Men/women (n) | 7/5 | 7/5 |
| Age [yr; median (range)] | 63 (58–67) | 64 (57–66) |
| Weight [kg; median (range)] | 95 (56–140) | 97 (71–125) |
| Height [cm; median (range)] | 177.5 (169–196) | 178 (168–194) |
| Duration of disease | | |
| Diabetes mellitus [yr; median(range)] | 12 (3–35) | 11 (2–45) |
| Neuropathic pain [yr; median (range)] | 6 (1–10) | 6.5 (2–25) |
| Affected limbs | | |
| Legs (n) | 8 | 8 |
| Legs+arms (n) | 4 | 4 |
| Medication | | |
| Insulin | 8 | 6 |
| Metformin | 11 | 7 |
| Pregabalin | 3 | 2 |
| Duloxetine | 2 | 0 |
| Amitriptyline | 1 | 1 |
| Steroid | 0 | 2 |
| Paracetamol | 1 | 1 |

Results

Eighty-seven patients responded to the advertisement (Fig. 1). Thirty-one decided not to participate after they were informed on the nature of the study. Thirty-one others were excluded because of the absence of pain, diabetes, or neuropathy (as assessed by QST), not meeting age- or BMI-related inclusion criteria, the use of strong opioids, or their inclusion in another trial. Twenty-five subjects were enrolled in the study and randomized. One patient retracted her consent after randomization; she was replaced by another subject. The patient characteristics of the participating patients are given in Table 1. All patients completed the study without major side-effects. QST measurements obtained from affected hands and feet are presented in Figure 2. The patients presented with a mixed small and large fibre neuropathy as evidenced

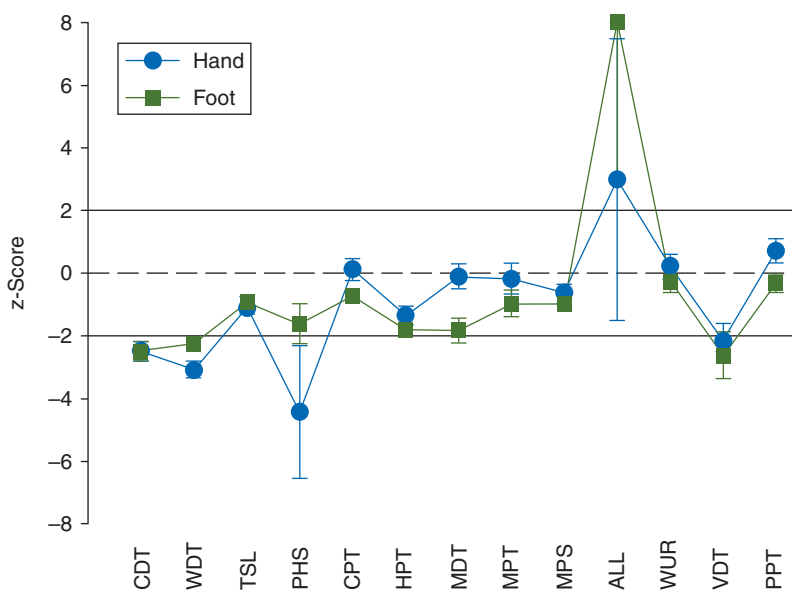


Fig 2 Results of the QSTs obtained on the affected skin areas (hand/feet). The data are the populations mean z-scores (SEM). z-Scores were calculated in relation to a population of healthy subjects as determined by Rolke and colleagues.²⁰ z-Values above the broken line indicate a gain of function, whereas values below this line are indicative for a loss of sensory function. CDT, cold detection threshold; WDT, warm detection threshold; TSL, thermal sensory limen; PHS, paradoxical heat sensations; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; ALL, dynamic mechanical allodynia; WUR, wind-up ratio; VDT, vibration detection threshold; PPT, pressure pain threshold.

by reduced cold and warm detection thresholds and paradoxical heat sensation (signs of small fibre involvement) and a reduced vibration detection threshold (on the feet more than on the hands; a sign of large fibre involvement). Importantly, allodynia was observed in seven (of 24) patients. During the study period, the daily drug dose was titrated to a level with sufficient analgesic effect and acceptable side-effects to the patients. In the placebo group, the maximum daily dose of 500 mg day⁻¹ was reached in all subjects compared with an average of 433 (31) mg day⁻¹ in the tapentadol SR group.

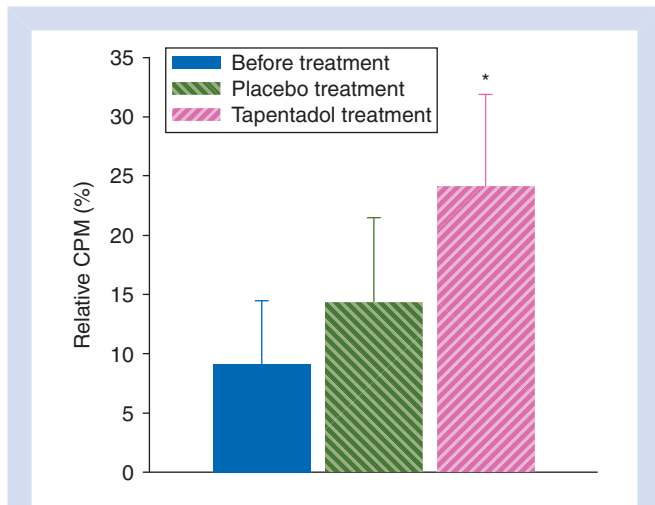


Fig 3 Relative CPM responses at baseline (before treatment), in patients receiving a 4-week placebo treatment, and patients receiving a 4-week tapentadol treatment. At baseline, the effect of the CS was not significant ($P=0.09$). During placebo and tapentadol treatment, the effect of the CS was significant (placebo $P=0.04$, tapentadol $P<0.01$). A treatment effect was present with greater increase in CPM responses during tapentadol treatment than during placebo treatment ($*P<0.001$ vs placebo).

Reported side-effects were nausea (placebo: $n=4$; tapentadol: $n=3$), vomiting (placebo: $n=0$; tapentadol: $n=2$), sedation (placebo: $n=2$; tapentadol: $n=6$), dizziness (placebo: $n=2$; tapentadol: $n=6$), and dry mouth (placebo: $n=1$; tapentadol: $n=5$).

Before treatment, significant CPM responses were not detectable as the effect of the CS was not significant [CPM=9.1 (5.4)%, $P=0.09$, Fig. 3]. After both treatments, CPM responses increased to significant levels [placebo: CPM=14.3 (7.2)%, $P=0.04$; tapentadol SR: CPM=24.2 (7.7)%, $P<0.01$]. A clear treatment effect was present with tapentadol SR CPM responses greater than placebo responses ($P<0.001$, Fig. 3).

Weekly pain scores after tapentadol and placebo treatments are given in Figure 4A. It shows a clear distinction in pain reduction in weeks 3 and 4 of treatment with greater analgesia in patients treated with tapentadol SR [pain scores at baseline 6.5 (0.6) reduced to 4.8 (0.7) after placebo and 3.9 (0.6) after tapentadol; 4-week treatment effect, $P=0.03$]. Plotting pain relief vs CPM responses shows that greater pain relief from tapentadol SR coincided with enhanced CPM responses (Fig. 4B).

OA responses before tapentadol treatment and at week 4 of treatment are given in Figure 5. As contrast, an example of an OA response in age- and sex-matched healthy volunteer is added in Figure 5A (data from Niesters and colleagues).¹⁹ Δ eVAS values in healthy volunteers in the age cohort 40–80 years range between 90% and 100%, irrespective of sex.¹⁹ Before treatment, Δ eVAS was 40.7 (7.4)%. Neither placebo [change from baseline +2.6 (11.6)%] nor tapentadol SR treatment [change from baseline -0.8 (3.7)%] had an effect in the magnitude of OA (treatment effect, $P=0.78$).

Discussion

Tapentadol is a new centrally acting analgesic agent for treatment of acute and chronic pain,^{11 23–26} which acts through MOR agonism and neuronal norepinephrine reuptake

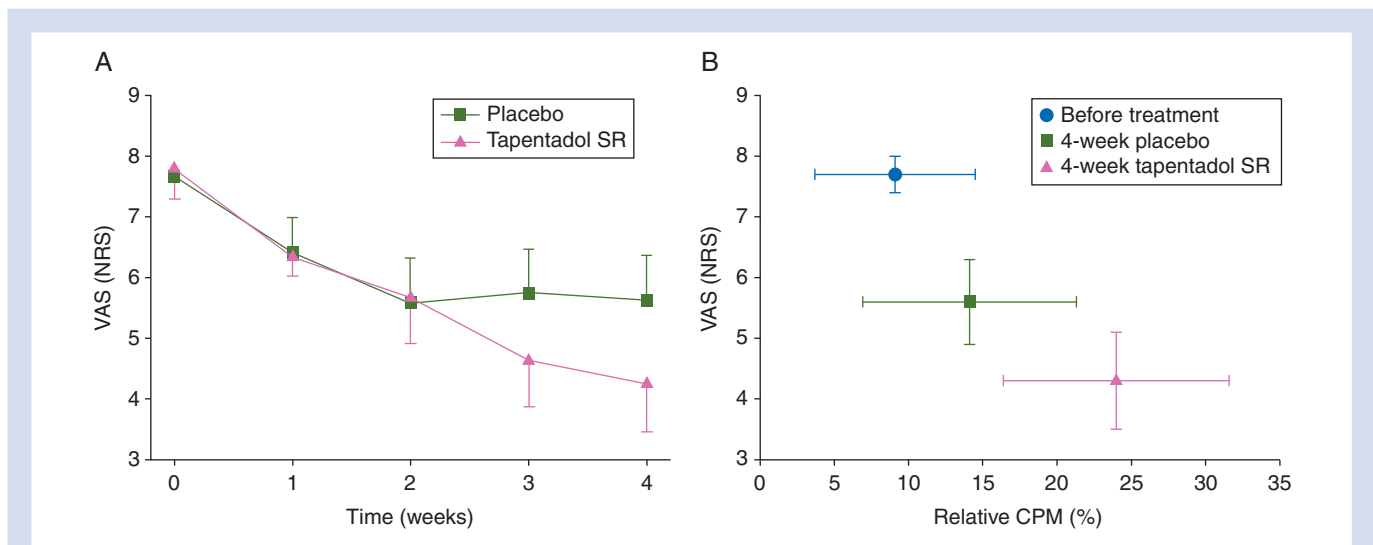


Fig 4 (A) Average spontaneous pain scores of DPN patients during the 4-week treatment period. There was a significant treatment effect with greater pain relief during tapentadol treatment ($P=0.03$). (B) Relative CPM responses vs pain scores. Values are mean (\pm SEM).

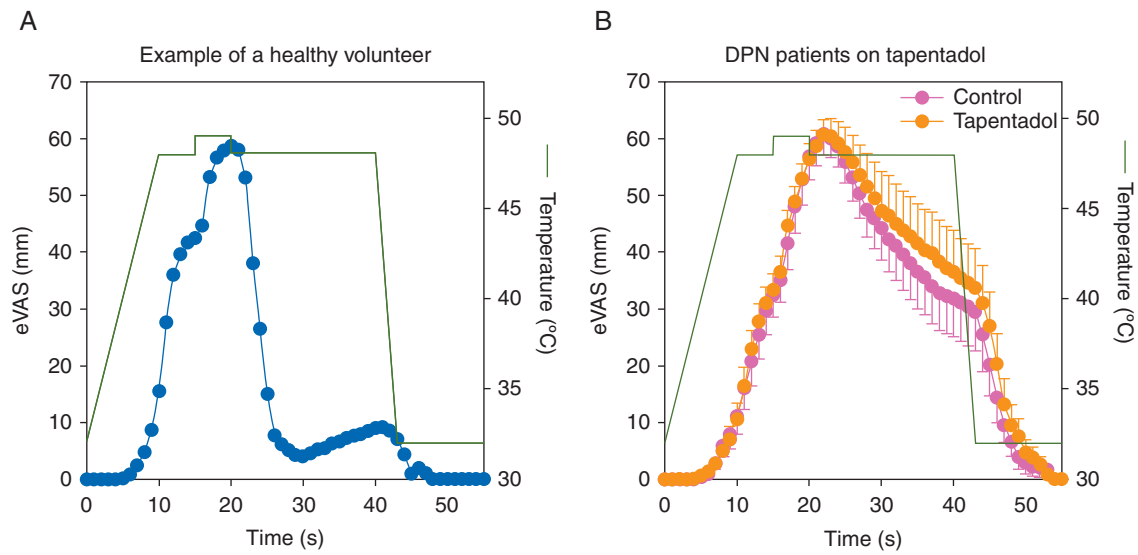


Fig 5 OA responses. (A) An example of a healthy volunteer (female, 60 yr). Data taken from Niesters and colleagues.¹⁹ (B) Absence of tapentadol treatment on OA in painful diabetic neuropathy patients.

inhibition (NRI).^{8-9 21} Through this combined mechanism of action, it is thought that tapentadol engages and potentiates descending pain inhibitory pathways,¹¹ although there are no human studies to substantiate this. We studied tapentadol's effect on two experimental paradigms of endogenous pain modulation (CPM and OA) in chronic pain patients with DPN. The main findings of our studies are that in DPN patients, tapentadol SR caused significant pain relief that coincided with enhanced CPM responses. No effect of tapentadol was observed on OA responses. Taking these results, we reason that relief of chronic pain in DPN patients by tapentadol is associated with engagement and potentiation of descending inhibitory pain pathways.

Conditioned pain modulation

Modulation of pain in humans involves activation of higher cortical centres (prefrontal cortex, anterior cingulate cortex, insula), brainstem (periaqueductal gray, rostral ventromedial medulla), and descending pathways projecting to the dorsal horn of the spinal cord.^{1 22 27} These descending pathways may be inhibitory or excitatory. Consequently, nociceptive input that enters the spinal dorsal horn will undergo some form of modulation, either facilitation or inhibition, which results in an amplified or inhibited pain sensation at central sites. Various chronic pain syndromes show loss of descending pain inhibition, including fibromyalgia, irritable bowel syndrome, chronic tension headache, temporomandibular disorder, complex regional pain syndrome, and chronic pancreatitis.²⁻⁵ Of importance is the finding by De Felice and colleagues²⁸ who showed in rodents that a genetic predisposition to activate descending inhibition protects against the development of chronic pain after peripheral nerve damage. In humans, examples of efficacious engagement of descending

inhibitory pain modulation include placebo analgesia, stress-induced analgesia, and CPM.^{15-17 29 30} CPM is an experimental and consequently surrogate tool used to quantify descending pain inhibition in humans. Central inhibition of a focal noxious stimulus is induced by the administration of a noxious stimulus at a remote area (CS), thereby reducing the perception of the focal or test pain stimulus ('pain inhibits pain').^{12 15} The central nature of CPM has been ascertained by the observation that specific brain regions involved in descending inhibition are activated during CPM tests in volunteers.^{31 32}

Volunteer studies show that CPM engagement is less effective in women relative to men and that CPM efficacy is reduced in elderly people (starting at middle-age).^{33 34} Indeed, in our middle-aged DPN patient population (mean age 59 yr), CPM was not present before the intake of study medication. Whether this is related to the underlying disease or an age-effect is unknown. Irrespective, individuals that are less able to activate CPM may have a higher probability of chronic pain development after a specific insult such as peripheral nerve damage from diabetes (cf. De Felice and colleagues)²⁸ or surgery. Yarnitsky and colleagues¹⁶ showed that patients with less efficient CPM responses were at risk for development of chronic post-thoracotomy pain. The method of induction of CPM has been validated previously by us in healthy volunteers and is applied by others in chronic pain patients.^{14 16}

Taking its mechanisms of action, tapentadol will interact within the descending modulatory system by activation of MORs and inhibition of neuronal norepinephrine reuptake.^{7 8} Both neurotransmitter systems play an important role in the activation of descending inhibitory pain pathways at supraspinal sites and in the spinal dorsal horn (at pre- and postsynaptic sites). See Ossipov and colleagues¹ for an excellent review on this topic. For example, animal studies show that activation of MORs on brainstem nociceptive 'on-cells' will release the

inhibition of brainstem nociceptive 'off-cells' that project to the spinal dorsal horn where nociceptive signal propagation is subsequently inhibited.¹ Activation of spinal dorsal horn pre- and postsynaptic α_2 -adrenergic receptors will cause potent analgesic responses by inhibiting nociceptive afferent input. Such analgesic effects are observed after the intrathecal administration of the postsynaptic α_2 -adrenergic receptor agonist clonidine.³⁵ Although tapentadol displays weak MOP-receptor affinity in chronic pain, animal studies show that its synergistic effect at MOP- and adrenergic-receptor systems will cause potent analgesic responses.^{6 9 21} Indeed, animal studies and clinical trials show that tapentadol is an effective analgesic in a variety of chronic pain syndromes (e.g. osteoarthritis pain, low back pain, neuropathic pain).^{8 11 26 36 37}

We observed that the analgesic efficacy of analgesic treatment (tapentadol/placebo) was coupled to its effect on CPM (Fig. 4). A 4-week treatment with placebo caused small analgesic effects (Δ NRS=1.7 cm) coupled to a modest increase in CPM (+14.3%), while tapentadol treatment caused a larger analgesic response (Δ NRS=3.9) coupled to a large CPM response (+24.2%). This later CPM value is similar to those observed in young healthy volunteers.¹³ These findings support a mechanistic role for the endogenous analgesia system in producing effective pain relief by tapentadol, possibly by its synergistic effect at MOP and α_2 -adrenergic receptors (see above). Yarnitsky and colleagues¹⁷ showed a coupling between drug efficacy and magnitude of CPM responses for duloxetine, a serotonin-norepinephrine reuptake inhibitor (SNRI), in DPN patients with initially less effective CPM responses. While our small patient population, with initially minor or absent CPM responses, benefited from the 4-week tapentadol SR treatment, we remain uninformed on the efficacy of tapentadol in chronic pain patients with 'normal' CPM responses (i.e. responses of similar magnitude to those observed in young and healthy volunteers). Extrapolating the duloxetine data from Yarnitsky and colleagues would suggest that tapentadol is less effective in these patients. There is now ample evidence to argue that in painful neuropathy patients with absent or reduced CPM, CPM responses may be reactivated or potentiated by analgesic treatment that targets one or more components of the endogenous pain modulatory system.^{4 17}

In chronic pain patients, the effect of tapentadol SR requires several weeks to develop (Fig. 3). Similar observations have been made for other S(N)RI-type of analgesics and tricyclic antidepressants.³⁸ Hence, it is recommended to evaluate the start of pain therapy with these agents not earlier than after 2 weeks of treatment.³⁹ Taking the similarities of mechanisms of action among these analgesics, we argue that the slow accumulation of norepinephrine at its putative effector sites may be held responsible for its slow onset of action. Our findings stress the importance of the noradrenergic component in inducing tapentadol analgesia in chronic pain as was earlier observed in animal studies.⁸

Two patients in the tapentadol group used duloxetine (duration of treatment >1 yr), a serotonin and norepinephrine reuptake inhibitor, without opioidergic activity. Theoretically, the use of this drug may have enhanced the CPM responses

induced by tapentadol. However, before tapentadol treatment, these patients had no detectable CPM response and the magnitude of their CPM response after the 4-week tapentadol treatment was well within the range observed in patients not on duloxetine. We argue that these two patients did not confound the results of our study.

Offset analgesia

OA is a relatively novel model of endogenous analgesia that produces temporal alterations in pain processing. The phenomenon occurs when a small decrease (1°C) in temperature during noxious stimulation evokes a disproportionately large decrease in pain perception.^{18 19} We previously assessed OA responses in a large population of volunteers aged 6–88 yr and observed response values ranging from 92% to 99%. It has been suggested that OA is of central origin as functional imaging studies show that OA activation coincides with activation of brain regions involved in the central modulation of pain.⁴⁰ However, it cannot be excluded that OA is initiated by dynamic responses of primary afferents or spinal processes. For example, Darian-Smith and colleagues⁴¹ reported that in monkeys, the discharge of heat-sensitive nerve fibres innervating the skin was nearly completely suppressed during a 10 s 1°C cooling pulse from a baseline temperature of 39°C. A similar mechanism may occur during OA activation. A peripheral origin of OA is further supported by the observation that central acting drugs such as opioids (tapentadol, morphine, remifentanyl), opioid antagonists (naloxone), and *N*-methyl-D-aspartate receptor antagonists (ketamine) are unable to affect OA responses in volunteers and neuropathic pain patients.^{14 19 42} Finally, a recent observation that while OA is present on the forearm of healthy volunteers, it is absent on the palm of the hand further suggesting that peripheral mechanisms are important in the development of OA.⁴³

We reproduce our earlier observation that OA responses are absent or reduced in patients with peripheral neuropathy.¹⁹ The Δ eVAS values observed in the DPN patients were about 40% of those previously observed by us in healthy volunteers of the same age and sex.¹⁹ No improvement or alteration of OA responses was observed after the 4-week tapentadol treatment, which indicates that this phenomenon of endogenous analgesia is without opioidergic or noradrenergic involvement. However, it may well be that the large and small nerve fibre damage that was present in our current population prevented their ability to discern small changes in skin temperature and consequently prevented peripheral activation of OA.

In conclusion, our results show that patients with DPN that display absent CPM responses benefit from tapentadol causing pain relief coupled to (re)activation of descending inhibitory pain pathways.

Authors' contributions

M.N. was involved in the writing of the protocol, performed the experiments, performed the data analysis, and wrote the paper. P.L.P. assisted with the experiments. L.A. assisted with the writing of the paper. E.Y.S. was involved in the writing of

the protocol and assisted with the writing of the paper. A.M.D. assisted with data analysis and writing of the paper. A.D. wrote the protocol, assisted with data analysis, and the writing of the paper.

Declaration of interest

A.D. and A.M.D. received speakers fee from Grünenthal. The other authors declare no conflicts of interest.

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