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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 disproportionally 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 disproportionally 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 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).

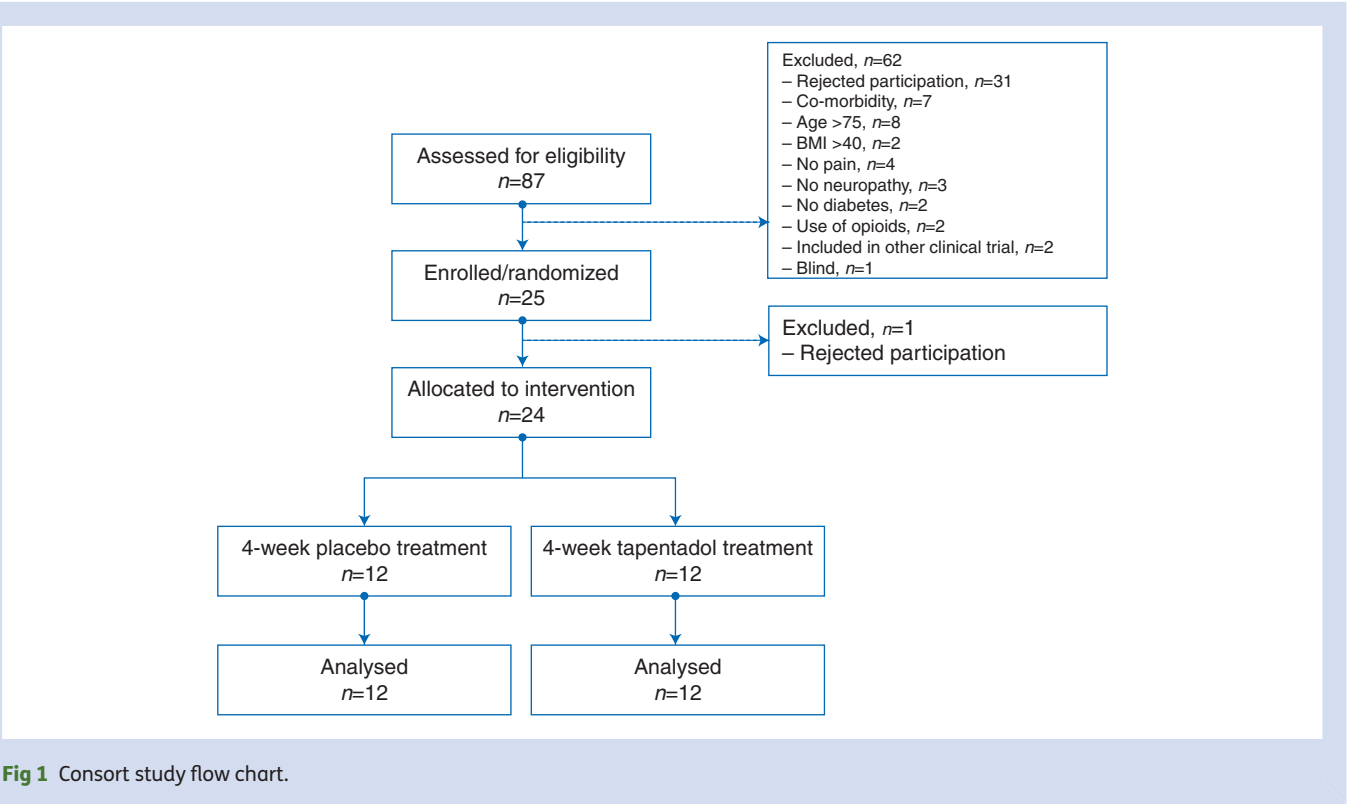

Fig 1 Consort study flow chart.