Open Access Full Text Article

REVIEW

Tapentadol for neuropathic pain: a review of clinical studies

Ulderico Freo[1]
Patrizia Romualdi[2]
Hans G Kress[3]

[1]Anesthesiology and Intensive Medicine, Department of Medicine DIMED, University of Padua, 35100 Padua, Italy; [2]Department of Pharmacy and Biotechnology, Alma Mater Studiorum-University of Bologna, 40126, Bologna, Italy; [3]Department of Special Anaesthesia and Pain Medicine, Medical University/AKH of Vienna, Vienna, Austria

Abstract: Neuropathic pain (NP) is an enormous burden for patients, caregivers and society. NP is a pain state that may develop after injury of the peripheral or central nervous system because of a wide range of diseases and traumas. A NP symptom component can be found also in several types of chronic pain. Many NP patients are substantially disabled for years. Due to its chronicity, severity and unpredictability, NP is difficult to treat. Tapentadol is a central-acting oral analgesic with combined opioid and noradrenergic properties, which make it potentially suitable for a wide range of pain conditions, particularly whenever a NP component is present or cannot be excluded. In randomized controlled trials, tapentadol has proved to be effective in relieving NP in diabetic peripheral neuropathy and in chronic low back pain. In observational studies, tapentadol reduced NP in chemotherapy-induced peripheral neuropathies, blood and solid cancers, and the NP component in neck pain and Parkinson's disease. This narrative review aims to provide clinicians with a broad overview of tapentadol effects on NP.

Keywords: neuropathic pain, tapentadol, pain therapy

Introduction

Neuropathic pain

Neuropathic pain (NP) has been defined as a "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system".[1–4] NP results from maladaptive neuroplastic responses that follow a "damage" to the nervous system from a large range of potential causes (ie, peripheral neuropathies, spinal cord injuries, and brain lesions). NP is characterized by spontaneous pain in the absence of sensory stimuli and almost always by a variety of symptoms of sensory loss (ie, hypoesthesia and hypoalgesia) and/or sensory gain (ie, tactile and mechanical allodynia).[1–4] As no gold standard exists, a grading system has been proposed and revised to provide a level of diagnostic accuracy from unlikely NP to possible, probable and to definite NP. This is based on the plausibility of the neuroanatomic distribution of pain symptoms and sensory abnormalities, and on the demonstration of their relationship with a nervous system lesion by diagnostic confirmatory tests (ie, neurophysiological testing and/or neuroimaging).[1–4] History of NP and objective sensory disturbances are required for diagnosis of probable NP and treatment.[1–4]

However, NP may not be an all-or-nothing event associated with specific neurological conditions but rather a part of a spectrum of chronic pain where pain can be "more or less neuropathic" in different clinical conditions.[5,6] While it

Correspondence: Ulderico Freo
Anesthesiology and Intensive Medicine, Department of Medicine DIMED, University of Padua, Via Giustiniani, 2, 35100 Padua, Italy
Tel +39 049 821 3090
Fax +39 049 875 5093
Email ulderico.freo@unipd.it

has been designed for patients undergoing diagnostic assessment for characteristic neurological lesions (ie, diabetic painful neuropathy, and multiple sclerosis), the NP grading algorithm may not work so well in disorders with mixed pain, nociceptive pain and NP, which represent the most commonly encountered pain conditions in clinical practice (ie, cancer pain, low back pain, post-traumatic and post-surgical pain).[7,8] In these patients, it may be difficult or impossible to confirm a neurological lesion and reach diagnostic accuracy (ie, probable or definite NP) required for NP treatment.[7,8] NP grading has been used more in research than in the clinical setting, and has not yet been advocated by IASP.[2,7,8] As a consequence, a substantial number of patients with mixed pain may not receive appropriate treatment for NP.[7,8] In order to prevent a significant number of patients from not receiving an appropriate treatment, revisions of IASP diagnostic criteria for NP are being proposed.[2,7,9]

In clinical practice, as Bouhassira and Attal[7] pointed out, the pain features are diagnosed before the identification of the underpinning tissue and neural lesions, and may guide treatment.[7] NP patients report a small and consistent group of sensory abnormalities (see above), which suggest that, in spite of their different etiologies, NP conditions may share common pathophysiological mechanisms.[3,7] Based on patient NP descriptors and to circumvent practical difficulties of NP diagnostic grading in a non-specialist environment, several questionnaires have been developed and validated as NP screening and assessment tools.[3,7] The Neuropathic Pain Symptom Inventory (NPSI) and painDetect questionnaire (PDQ) depend entirely on patient self-report; and Signs scale in the Leeds Assessment of Neuropathic Symptoms (LAANS) and Douleur Neuropathique en 4 Questions (DN$_4$) rely on interview responses and on physical findings.[3] Although less accurate than the NP grading system, NP questionnaires have shown good sensitivity and specificity in validation studies; cut-off values have been set to indicate the probability of NP.[3,7] NP questionnaires are being used extensively to assess prevalence of NP at population level and in chronic pain conditions.[3,7]

Chronic NP and chronic pain per se are both highly disabling disorders. The prevalence of NP is estimated to be between 7% and 10% in the general population and many NP patients are significantly disabled for years from a moderate-to-severe pain.[10,11] Worldwide, chronic pain (ie, lasting longer than 3–6 months) affects at least 20% of people and encompasses five of the eleven top, leading

conditions for years lived with disability.[8,12] The prevalence of NP is up to 20–25% in patients reporting chronic pain when mixed pain is included; a significant NP component is thought to contribute to the considerable loss of quality of life (ie, altered cognition, mood, and sleep), employment, and increased healthcare and social costs caused by chronic pain.[3–5,10–19]

A high frequency of NP symptoms has been reported in neurological and rheumatological disorders that are not typically associated with NP conditions (ie, without identifiable neural correlates), such as motor neuron disease, Parkinson's disease, Alzheimer's disease, low back pain, knee and hip arthritis, and rheumatoid arthritis.[3,5,20–32] In these conditions, nociceptive pain and inflammatory pain are due to activation of nociceptors from tissue damage and/or from release of inflammatory mediators because of abnormal postures, muscle rigidity, constipation, and/or joint tissue inflammation.[20–32] It not clear yet whether NP symptoms are caused by chronic nociceptive pain itself via a peripheral and/or central sensitization process, which may include activation threshold shift, upregulation of voltage-gated sodium channels, N-methyl-D-aspartate-type glutamate receptor and neuropeptide receptor activation, but no neural lesion.[5] Alternatively, however, in rheumatological conditions NP has been postulated to be due to somatosensory lesions, such as loss of nerve terminals and/or ectopic innervation, which have been described in articular and periarticular tissues; much alike, in neurodegenerative disorders, changes of the peripheral and central somatosensory system have been pathologically identified and linked to NP.[24–28] When a neural lesion can be only hypothesized and not demonstrated, the occurrence of NP symptoms has been variously labeled as "NP component," "NP mechanisms," "NP-like phenotype," "pain with NP features,", or "NP symptoms."[8,27,33]

However, whatever the cause, it is clinically relevant that patients with a high probability of NP present with higher comorbidity and with a poorer quality of life and surgical outcome than their counterparts with a low level of NP symptoms.[24,27,28,33–35] Untreated NP may cause trials to fail and, conversely, treating NP symptoms with antineuropathic agents may be beneficial to patients.[3,5–21] The efficacy of currently available pharmacological and non-pharmacological treatments for NP are limited with randomized controlled trials (RCTs) reporting only a 30–48% benefit rate with active treatment compared with 11–30% with placebo.[21–25] The number of patients reporting a clinically meaningful pain relief (ie, commonly at least

50% decrease of pain intensity) with any treatment is low, usually 10–25% more than with placebo. Preclinical and clinical studies indicate that NP is associated with hyperexcitabiliy of pain ascending pathways and to decreased pain modulation by descending noradrenergic pathways.[15,19] For NP, recent guidelines place NRI antidepressants among first-line drugs that may strengthen descending inhibitory pain controls.[15,19] Opioids act mostly by inhibiting ascending pain pathways and are recommended as second- or third-line treatments for NP.[15,19] For nociceptive pain, NSAIDs and acetaminophen are the first-line treatments but they are often limited by lack of efficacy and potential life-threatening side effects, especially in older patients.[36] Opioids should be considered in all patients with chronic moderate-to-severe nociceptive pain and with pain-related impairment of functions and quality of life, and for whom NSAIDs are contraindicated or ineffective.[36] Therefore, a dual action, anti-neuropathic and -nociceptive agent may be particularly advantageous in clinical conditions with a mixed, nociceptive and neuropathic pain, which is a common pain state in the clinical practice.[8]

Tapentadol

Tapentadol is a strong analgesic with a unique dual mechanism of action that combines μ-opioid receptor agonism (MOR) and norepinephrine reuptake inhibition (NRI), and has been proposed to be the first representative of a new class of drugs, the MOR-NRI agents (μ-opioid receptor agonists and norepinephrine reuptake inhibitors).[37–39] The MOR mechanism interrupts pre- and post-synaptic transmissions of ascending pain signals in the spinal cord and activates the descending inhibitory projections supraspinally, while NRI increases synaptic norepinephrine and enhances the descending inhibitory tone (Figure 1).[27,30,31] NRI drugs are known to be useful in chronic NP.[15,18,37,40] Interestingly, experimental and clinical evidence indicates that the NRI component of tapentadol may become predominant in NP conditions.[37,39–43] In addition, the NRI activity of tapentadol has the potential to counteract the adverse MOR-mediated effects on hippocampal neurogenesis, thus resulting in less or no dysfunction in adult neurogenesis and associated functions, such as memory.[44] Finally, tapentadol shows minimal serotoninergic activity, which is important in the prolonged management of patients, since serotoninergic pathways may promote pain and nausea.[39]

Therefore, the use of tapentadol could expand the pharmacological armamentarium against NP, which is often challenging to treat with other analgesics or co-analgesics, such as
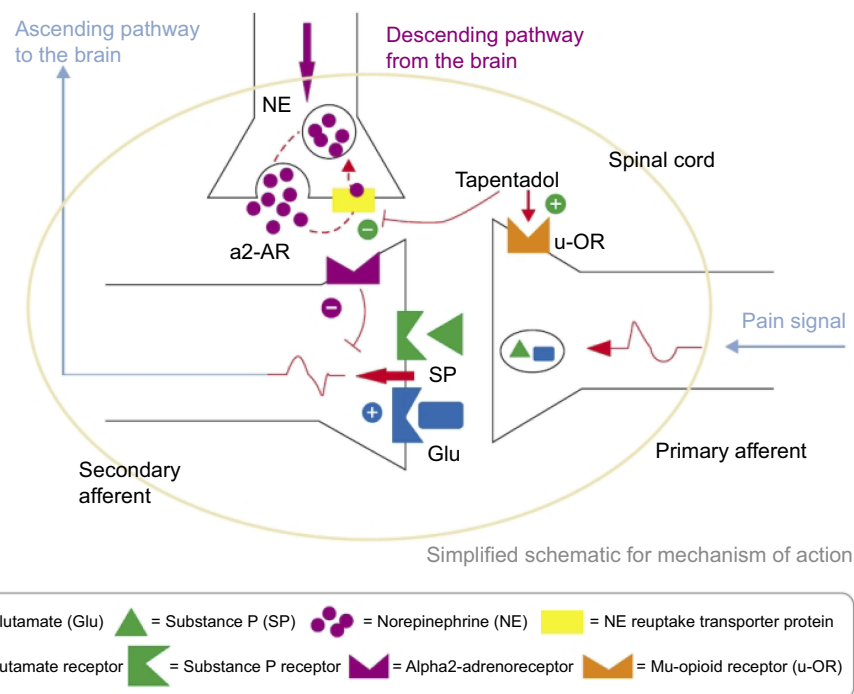

Figure 1 Schematic drawing of the dual mode action of tapentadol. Reproduced with permission from Chang EJ, Choi EJ, Kim KH. Tapentadol: can it kill two birds with one stone without breaking windows? *Korean J Pain*. 2016 Jul;29(3):153–157.[41]

antidepressants or anticonvulsants.[45–50] In phase III studies, tapentadol has been shown to be effective and well tolerated for the management of moderate-to-severe chronic pain, of either non-oncological and oncological origin.[37,38,51–54]

In spite of its therapeutic potential, there have been only a few randomized control trials (RCTs) on tapentadol's antineuropathic activity. However, in observational studies, the effects of tapentadol have been reported on secondary outcome measures of NP associated with different clinical conditions. Patients were treated by hematologists, neurologists, oncologists and pain specialists over a 3–6-month period (see below). This is a narrative review of existing evidences on the effects of tapentadol in chronic NP (see Table 1 for an overview).

Search strategy and study selection

Our aim was to report evidence from the available literature of antineuropathic properties of tapentadol. We searched for articles in EMBASE, MEDLINE and PubMed, with the terms "tapentadol" and "neuropathic," "DN$_4$," "LANSS," "PainDETECT," "Neuropathic Pain Symptom Inventory," "McGill Short Form Pain Questionnaire." We only included human studies that assessed the effects of tapentadol on NP measures. Some relevant features of the studies (ie, author, clinical condition, methodology, patient numbers, pain and NP outcomes) are reported in Table 1. All studies evaluated tapentadol extended or prolonged release (PR).

Tapentadol in painful peripheral neuropathies

Painful peripheral neuropathies (PPN) are a group of the peripheral nervous system disorders with heterogeneous etiologies (ie, genetic, inflammatory, metabolic, toxic and traumatic).[55] PPN are the most frequent NP conditions that impair physical and mental functions and that may, eventually, affect quality and expectancy of life.[1–4,55–67] While the prevalence of postherpetic neuralgia (PHN) is expected to decrease thanks to vaccination, diabetic peripheral neuropathy (DPN) and chemotherapy-induced neuropathy (CINP) are likely to increase because of the epidemics of obesity and diabetes and because of improved survival of cancer patients, respectively. In total, 25% of diabetics develop DPN. Worldwide, the number of people with diabetes has quadrupled in the last 30 years to 422 million people and a prevalence of 8.5%.[64] CIPN is the major dose-limiting adverse event by cancer chemotherapy with platinum agents, taxanes, vinka alkaloids, thalidomine and bortezomid; CINP pain may last a long time and force treatment discontinuation, eventually impacting on rehabilitation and survival.[66,67]

Both central and peripheral mechanisms are involved in DPN, including polyol pathway hyperactivity, Na$^+$-channel proliferation in peripheral nerves, microvascular nerve ischemia, altered Schwann cells, abnormal thalamic activity and impaired descending inhibitory function in the central nervous system.[68–71] Studies on PHN and CINP have focused on pathological changes in dorsal root ganglia and nerve endings. CINP pathophysiology has not been fully elucidated. Taxanes may cause NP by disrupting mitochondrial energy production and axoplasmic flow.[72] However, in contrast to initial reports of poor drug entry, taxanes also enter the central nervous system and, that way, may cause altered sensation and pain.[66,67]

Monotherapy with non-opioid or opioid analgesics provides insufficient relief, and therefore combinations therapies with different classes of drugs are tried.[18,37,45,46,56,59] Although effective, opioid analgesics are considered a second-line treatment in this setting due to their overall poor tolerability and safety profile including the potential risk of abuse or misuse in the long run.[46,56,73–75] In experimental and clinical DPN, NRI antidepressants improve NP by enhancing or restoring the noradrenergic descending inhibitory pathways.[19] The NRI mechanism of tapentadol action appears to be dominant over the MOR activity in chronic NP.[37,39–43] Hence, because of its dual mechanisms of action and in particular its NRI component, tapentadol may be beneficial to PPN.[39–43]

Postherpetic neuralgia

Tominaga et al reported a 12-week (ie, ≤6-week titration plus maintenance periods), double-blind, placebo-controlled RCT on 31 patients treated with tapentadol extended release (ER) for PHN or DPN (mean dose 274.5±148.3 mg/day).[58] The last observation carried forward (LOCF) was used for imputing missing pain intensity data for the primary endpoints, which were then analyzed using the analysis of covariance (ANCOVA) on all patient populations (intention to treat [ITT]). In a subset of 13 PHN patients, tapentadol PR was not superior to placebo.[58] Pain Numerical Rating Scale (NRS) declined from pretreatment to treatment week 12 from 7.0±1.4 to 5.0±2.9 in the placebo group and from 6.7±0.9 to 4.5±2.3 in the tapentadol group (mean reduction 2.0±2.4 and 2.2 ±2.2).[58] No difference was observed between placebo and

Table 1 Effects of tapentadol on neuropathic pain

Author	Study features					Tapentadol mean daily dose (mg)	Pain		Neuropathic pain	
	Condition	Patient number	Duration (months)	Type	Comparator		NRS/VAS decrease	Responders (%)	DN4/NPSI/PDQ decrease	Responders (%)
Musculoskeletal pain conditions										
Billeci[88]	CNP	44	3	PO		204.5±102.8	5.1	68^B	DN4, 2.2^B	47^dB
Baron[85]	LBP	130	3	RCT	Oxycodone	378.8±129.6	3.7		PDQ, 10.8	
Baron[83]	LBP	59 154 159	3	PO DB DB	Pregabalin	300 500 300	5.2 4. 4.2		PDQ, 12.3^B PDQ, 10.3^B PDQ, 11.0^B	
Passavanti[84]	LBP	55	6	R PO	Tapentadol-PEA	158.0±8.50 121.7±6.20	−1.8^A	68^cA	DN4, 1.8^A	28^cA
Tedeschi[61]	PAD	25	3	PO		186.4±56.0	5.1^B	80^a	DN4, 2.8^B	78^d
Ueberall[86]	LBP	133	3	R	Oxycodone	298.5±71.2	31.2^A −3.8^B	84^g −1.7	PDQ7, 5	42^a
Cancer pain conditions										
Sugiyama[103]	SC	30	2,1	R		100	3			
Brunetti[94]	HC	36	1	PO		243.5±105.6	7		DN4, 3.4	75^d
Coluzzi[93]	MM	25	3	PO		213.6±94.1	4,7		DN4, 4.3	100^d
Neurological pain conditions										
Galie[65]	CIPN	31	3	PO		200	3.4^B	86^a	DN4, 2.2^B	78^b
Vinik[59]	DPN	318	3	RCT	Placebo	100–250	0.95^A	40^Aa	NPSI, 8.84^A	
Niesters[43]	DPN	25	1	RCT	Placebo	433±31	0.8^A			
Schwartz[60]	DPN	196	3	RCT	Placebo	200–500	1.3^A	39^a		
Freo[102]	PD	21	6	R		206.3±102.7	2.5^B	48^a	PDQ, 6.3^B	100^f

Notes: Responders: [a]VAS/NRS ≥50% reduction; [b]DN4 >30% reduction; [c]VAS and/or DN4 2 point reduction; [d]DN4 2 point reduction; [e]PDQ7 reduction to <18; [f]PD reduction to ≤18; [g]low back pain intensity index. Statistics: ^A intergroup comparison, significantly different from placebo or oxycodone; ^B intragroup comparison, significantly different from baseline.
Abbreviations: CIPN, chemotherapy induced peripheral neuropathy; DN4, douleur neuropathique en 4 questions; DPN, diabetic peripheral neuropathy; HC, hematolocical cancer; LBP, low back pain; multiple myeloma; NPSI, Neuropathic Pain Symptom Inventory; NRS/VAS, 0–10 Numerical Rating Scale/0–10 Visual Analogue Scale; NP, neuropathic pain; PDQ, painDetect questionnaire; PDQ7, seven-item painDetect; PD, Parkinson' disease; PEA, palmytoilethanoamine; PHN, postherpetic neuralgia; PO, prospective observational; R, retrospective; RCT, randomized-controlled trial; SC: solid cancers.

treatment groups for the patient global impression of change and for responders at ≥30% and ≥50% pain reduction.[58] These negative and disappointing findings have been ascribed to study design factors such as study underpower, heterogeneity of patients contributed in small numbers by 33 study centers in Japan, potential genetic factors and high numbers of uncontrolled concurrent medications; the authors reported also an unusually high placebo response probably due to large expectations generated in the patients from the 2:1 (treatment:placebo) enrollment design.[58] Recently, in the context of a complex therapy including gabapentin 1800 mg/day, oxacarbazepine 600 mg/day and amytriptiline 20 mg/day, tapentadol 500 mg/day failed to relieve pain in a 68-year-old patient suffering from trigeminal PHN.[76]

Diabetic painful neuropathy

In the RCT on NP by Tominaga et al tapentadol PR failed to outperform placebo in the subset of 18 DPN patients.[58] From pretreatment to treatment end, pain NRS declined on average by 2.9±2.43 in the placebo group and 2.8±2.24 in the tapentadol PR group.[48] The study on DPN was flawed like that on PHN.[58]

Schwartz et al conducted a phase III RCT to evaluate safety and efficacy of tapentadol PR in 588 DPN patients poorly responsive (NRS ≥5) to previous treatments.[57] Enrolled subjects were titrated to an optimal dose of tapentadol PR (200/500 mg/day) over an open-label 3-week period. Then, patients (n=395) with ≥1-point reduction in pain intensity were randomly assigned to receive the identified optimum dose of tapentadol or placebo for a 12-week double-blind phase.[57] The primary efficacy outcome was the change in average pain NRS. The mean change in average pain NRS from the start of double-blind treatment to week 12 was 1.4 in the placebo group and 0.0 in the tapentadol PR group (ANCOVA analysis on ITT and LOCF population).[57] Overall, the mean difference between groups in the change of average pain NRS from initiation of the double-blind phase to week 12 was −1.3 (95% CI: −1.70 to −0.92, P<0.001). In total, 61% (356/588) of patients reported a ≥30% improvement in pain intensity during the open-label phase; among patients randomized to tapentadol PR, 54% (105/196) reported a ≥30% improvement from the initiation of the study to week 12. No new safety signals were reported.[57]

These findings were corroborated by another RCT with a very similar design.[59] In this trial, a total of 358 patients completed the titration period; of these, 166 were assigned to tapentadol PR and 152 to placebo.[59] Mean pain on a 0–10-point NRS was 7.33±1.30 at the start and 4.16±2.12 at week 3 of the open-label titration period; mean change in average pain NRS from the start to week 12 of double-blind treatment was 1.30±2.43 in the placebo group and 0.28±2.04 in the tapentadol PR (ANCOVA on ITT and LOCF data). The mean difference in pain intensity from the initiation of the double-blind treatment to week 12 between tapentadol PR and placebo was −0.95 (95% CI: −1.42 to −0.49, P<0.001).[59]

In 2015, Schwartz et al performed a pooled analysis of the two comparable, above-mentioned studies in DPN patients.[60] The reported median duration of exposure to tapentadol PR during the double-blind maintenance period was 84 days. The median daily dose of tapentadol PR was 400 mg during this period.[50] Mean changes in pain intensity from baseline to week 12 of maintenance in the placebo (n=343) and tapentadol PR (n=360) group were 0.08±1.87 and 1.28±2.41, respectively, with a least squares mean difference of −1.14 (95% CI: −1.43 to −0.84, P<0.001), favoring tapentadol PR. Interestingly, this advantage of tapentadol was observed across different patient subgroups (ie, age, gender, ethnicity, opioid experience and pain intensity), and was paralleled by improved quality of life. Similarly, an advantage for tapentadol PR was observed in terms of response rates.[60] In conclusion, the pooled results showed that tapentadol PR is effective in the management of DPN-related pain, with consistently robust analgesic efficacy across different patient subgroups.

Niesters et al performed an interesting double-blind, mechanistic RCT in 24 DPN patients who received either placebo or tapentadol sustained release (SR) for 4 weeks.[43] Patients were selected from a group of 81 patients if they had at least two of the following symptoms in legs, arms or both (in a stocking-glove distribution): 1) symmetrical dysesthesias or paresthesias; 2) burning or painful feet with night-time worsening; or 3) peripheral tactile allodynia; and 4) an abnormal warm or cold detection threshold, an abnormal warm or cold pain threshold, or allodynia at the Quantitative Sensory Test.[43] Then, patients were assessed before treatment and weekly up to week 4 of treatment with a 0–10 pain Visual Analogue Scale (VAS) and with two functional measures of pain modulatory pathways, the conditioned pain modulation and the offset analgesia.[43] In comparison to placebo, tapentadol determined larger pain relief and larger conditioned pain responses.[43] From baseline to treatment week 4, pain VAS declined from 6.5±0.6 to 4.8±0.7 in the placebo

group and to 3.9±0.6 in the tapentadol SR group (ANOVA and two-tailed *t*-test analyses; *P*=0.03); in the same time, conditioned pain response increased from 9.1±5.4% to 14.3±7.2% with placebo treatment and to 24.2±7.7% with tapentadol (*P*<0.001). In comparison to placebo, tapentadol SR provided a larger correlated effect on pain and conditioned pain modulation suggesting that tapentadol SR improves NP by enhancing NRI pathways, that project from brainstem to spinal cord.[43]

Diabetic pain may include peripheral artery disease pain. In a study on 2,514 diabetics with pain in lower limbs, 9% had DPN alone, 8.5% had peripheral artery disease alone and 2.4% had both conditions which is named lower-extremity disease.[65] Peripheral artery disease can cause pain of mixed, nociceptive and neuropathic origin.[65] Therefore, analgesic treatment has to overcome both nociceptive and NP components of the pain. Given its dual mechanism of action, tapentadol may be considered suitable for this condition.[19,45,46,77] Tedeschi et al[61] investigated the effects of a 3-month therapy with tapentadol PR (final mean dose 186.4 ±56.0/day) in 25 diabetic patients with peripheral artery disease at lower extremities; 24 (96%) patients had also skin ulcers and 18 (72%) patients NP with intense paresthesia and allodynia (DN$_4$≥4).[61] In comparison to baseline, at month 3 of treatment pain NRS significantly declined from 7.9±1.2 to 2.8±2.3, DN$_4$ from 4.0±1.2 to 1.2±1.5 and the number of NP patients from 18 to four patients (72 vs 16%) (Mann–Whitney U test; *P*<0.01).[61] During treatment with tapentadol, the quality of sleep and the physical and mental components of SF-12 Health Survey improved significantly (*P*<0.01), suggesting the potential efficacy of tapentadol PR in this setting.[61]

Tapentadol for chemotherapy-induced neuropathy

In an open-label, 3-month, prospective study, Galiè et al assessed the efficacy of tapentadol in 31 patients with moderate-to-severe NP from a CIPN that was unresponsive to maximum doses of antineuropathic antidepressants, and anticonvulsivants.[62] CIPNs occurred after therapy with taxane (45%) or platinum agents (32%) or their combination for a solid tumor, mostly breast and digestive cancers (36 and 26%).[62] Tapentadol was titrated balancing pain relief and adverse events (final mean dose 200 mg/ day; personal communication). At baseline, all patients were classified as having NP according to DN$_4$ score.[62] From baseline to month 3 of treatment with tapentadol, the average DN$_4$ score declined from 6.36±1.4 to 4.18±0.73

(personal communication).[62] Nerve conduction values were unchanged from baseline to month 3 suggesting that tapentadol relieved NP *per se* without affecting or reversing peripheral nerve damage.[62]

Tapentadol in musculoskeletal conditions with a neuropathic component

According to the Global Burden of Disease reports 2010 and 2013, musculoskeletal conditions are the major causes of disability with chronic low back pain (CLBP) being the leading condition of disability, chronic neck pain (CNP) ranking fourth and other musculoskeletal conditions and osteoarthritis ranking tenth and thirteenth.[12] CLBP and CNP are classified as mixed pain syndromes that can have nociceptive and/or NP components.[78–88] Radicular NP from nerve root involvement is a frequent and typical NP component in CLBP and CNP. A NP symptom component, however, has also been reported in osteoarthritis and rheumatoid arthritis in the absence of overt nerve lesions.[27–32] In these painful conditions, NP has been ascribed to pathological changes of articular nerves.[28] Joint cartilage is poorly innervated in normal conditions but may undergo neurovascular invasion in osteoarthritis; in contrast, the highly innervated synovial membrane presents loss and plastic changes of nerve terminals.[27–33] Furthermore, in functional magnetic resonance imaging, CLBP patients with high PDQ scores presented with decreased cortical activation in response to painful stimuli, which suggests that CLBP may be associated to decreased descending inhibitory modulation of pain.[28–34,89,90] Although subtle pathological changes in peripheral and central nervous system are hard to be confirmed clinically, they still may explain sensory and neurological abnormalities including mechanical hyperalgesia and allodynia and loss of proprioception and vibration sensitivity, which are frequently found in osteoarthritis patients.[27–32,34]

The prevalence of a NP component in CLBP has been investigated in a number of studies, and the results varied significantly according to the method used for diagnosing neuropathic pain, ranging from 16.7% to 54.4%.[78] Freynhagen et al[78,79] using their PDQ found that 37% of 8,000 screened CLBP patients had a predominant NP component; when tested again by clinical, neurophysiological and imaging methods, PDQ had a positive predictive accuracy of 80–85%.[78,80] Using clinical judgement supported by neurophysiological and neuroradiological findings, LANSS

and PDQ, Liu et al found that mixed-to-definite NP can be diagnosed in 57–72% of CNP patients.[81] Patients with an identified NP component have been reported to experience more intense pain for a longer period of time than those without, and to have a higher prevalence of psychiatric comorbidities and disability.[78–80] However, not all clinical trials assessed the effects of tapentadol on the NP component in the more severe forms of CLBP and CNP; NP may be underdiagnosed and undertreated.

Tapentadol PR was evaluated in patients with severe CLBP with a NP component (ie, PDQ ≥12).[48] Patients received open-label (study IIIb) tapentadol PR (100–500 mg/day) for a 5-week titration and a subsequent 7-week maintenance period.[48] Tapentadol PR treatment was associated with significant improvements in NP symptoms in CLBP patients with a decreasing of both the numbers of pain attacks and the duration of spontaneous pain (mean PDQ decrease from baseline to study end 3.02 ± 2.07; $P < 0.0001$); interestingly, lower tapentadol doses were generally required with increasing likelihood of NP. These promising results have been corroborated by results obtained from an open-label continuation arm of a second, randomized phase IIIb study in patients with severe CLBP and a NP component (ie, pain NRS ≥6 and PDQ ≥12). All patients were titrated to tapentadol PR 300 mg/day over 3 weeks.[82] A subpopulation with pain intensity <4 continued receiving tapentadol PR 300 mg/day during an 8-week period.[82] For the primary study population, patients with ≥1-point decrease from baseline and pain intensity ≥4 were randomized to tapentadol PR 500 mg/day or tapentadol PR 300 mg/day plus pregabalin 300 mg/day during a concurrent 8-week, double-blind comparative period (observed case analysis by paired t-test).[82] The former subpopulation of patients with CLBP with a NP component responded very well to tapentadol PR 300 mg/day, with significant improvements in NP-related symptoms and quality of life (mean change from baseline to the end of titration in the EuroQoL-5D health status index score was 0.36 ± 0.370 and the mean change from baseline to the final evaluation was 0.39 ± 0.389; one-sample paired t-test on observed cases, $P < 0.0001$ for both measures).[82]

Passavanti et al evaluated the effects of adding on ultramicronized palmitoylethanolamide (PEA) to tapentadol in a subset of patients with CLBP and a NP component (ie, DN$_4$≥4 and hyperalgesia and allodynia by pinprick test and brush test).[83] These authors used a mixed prospective-retrospective design to compare the analgesic effects of PEA 600 mg twice a day added to background therapy with tapentadol in 35 patients in the prospective arm to

those of tapentadol alone in 20 patients of the retrospective arm.[83] Adding PEA synergistically augmented NP symptom relief by tapentadol. DN$_4$ scores at month 6 versus baseline showed that tapentadol/PEA patients achieved a significantly greater NP symptom relief than tapentadol patients.[83] Both groups achieved significant decrease the NP component over baseline (generalized linear mixed model and responder analyses, $P < 0.0001$), but the NP symptom reduction was significantly greater in the tapentadol/PEA than in the tapentadol group (ie, DN$_4$ from 6.1 ± 0.14 to 3.2 ± 0.13 and from 6.1 ± 0.09 to 5.0 ± 0.04, $P < 0.0001$).[83]

Baron et al carried out a 9-week, direct-comparison study between tapentadol PR and oxycodone/naloxone PR in patients with severe CLBP and a NP component (mean daily maintenance doses: tapentadol 378.8 ± 129.6 mg/day, oxycodone/naloxone 75.3 ± 24.3 mg/day).[84] At baseline, 74 and 76% of patients had a positive PDQ score (ie, >18, probable NP) in the tapentadol and in the oxycodone/naloxone group, respectively, and 25 and 21% had a PDQ unclear score (ie, 12–18, mixed pain).[71] Both tapentadol and the oxycodone/naloxone were associated to significant PDQ decrease from baseline to treatment end; however, tapentadol was associated with significantly larger reductions of PDQ.[84]

In a retrospective analysis, Ueberall and Mueller-Schwefe compared the analgesic effects of tapentadol versus oxycodone/naloxone in 261 CLBP patients randomly selected from a larger patient dataset of the Germany Pain Registry.[85] At pretreatment baseline, a subgroup of patients (109/261, 48%) presented probable NP (ie, PDQ$_7$ score ≥18). Tapentadol significantly reduced average PDQ$_7$ at week 12 compared with baseline as oxycodone/naloxone did (modified t-test on ITT and LOCF population; $P < 0.001$ for both treatments). From baseline to the final 12-week assessment, mean PDQ$_7$ scores fell from 17.7 ± 3.4 to 12.7 ± 5.2 in the tapentadol group and from 18.2 ± 3.7 to 12.4 ± 6.3 in the oxycodone group ($P < 0.001$ for both treatments).[85] At the same time, NP patients decreased from 47 to 20% in the oxycodone/naloxone group and from 37 to 22% in the tapentadol group. There was no difference in the effectiveness on NP between the two agents. The study has been criticized for the arbitrary selection of subsets of patients and for other relevant methodological biases.[86,87]

In an observational prospective study, tapentadol PR significantly ($P < 0.01$) reduced NP intensity from baseline to week in a subset of 54 CNP patients with moderate-to-severe chronic pain and NP- (ie, DN$_4$≥4) associated CNP.[88] The

average DN_4 score decreased from 4.1±2 at baseline to 1.9 ±2.1 at the end of week 12 (Bonferroni corrected ANOVA and *t*-test); in parallel, the percent of NP patients decreased from 70% (40/54) at baseline to 23% at study end (10/44). Treatment with tapentadol was associated with improved neck motion, and quality of sleep and life.[88]

Tapentadol in neuropathic cancer pain

NP can be encountered in every stage of cancer, from the preclinical stages of the disease until the end of life.[91–94] Cancer NP can result from a direct invasion/compression of the peripheral nervous systems, from an indirect paraneoplastic involvement or light chain amyloidosis, or as a consequence of therapeutic treatments (ie, surgery, radiotherapy and chemotherapy).[91–94]

Coluzzi et al retrospectively analyzed 25 multiple myeloma patients treated with tapentadol (final mean dose 213.6±94.1 mg/day) for moderate-to-intense pain.[92] At pretreatment assessment 18 patients (70%) presented NP, as assessed with DN_4.[92] Tapentadol was highly effective on NP symptoms reducing mean DN_4 score from 4.68 ±2.43 at baseline to 0.41±0.91 at week 12 of treatment and the numbers of patients with NP (Friedman test and McNemar test; $P<0.01$, for both measures); at the same time, all domains of SF-36 quality of life improved.[92]

Brunetti retrospectively analyzed the effects of tapentadol on 36 patients treated for 1 month because of blood malignancies.[93] At baseline, 56% of patients (20/36) presented NP according to DN_4. Tapentadol was slowly titrated to a final dose of 243.5±105.6 (personal communication). In comparison to pretreatment, at month 1 of treatment the NP patients decreased from 54 to 14%. Sleep quality improved to "good" or "refreshing" from 20% to 95% of patients.[93]

Tapentadol in aging and Parkinson's disease

Chronic pain is common and may affect up to 60% of elderly people aged 65 years or above.[95] Pain is most commonly a nociceptive musculoskeletal pain arising from degenerative joint disease (ie, osteoarthritis).[95] NP is common as well. In older adults, pain is often underdiagnosed and undertreated. Potential gastrointestinal and cognitive side effects of opioids are feared and limit their prescriptions. However, in the older patients, inadequate pain management increases risk for cognitive and functional impairment, depression, social withdrawal, and falls.[95]

Freo et al carried out a retrospective analysis on 96 patients with chronic musculoskeletal pain of moderate-to-severe intensity (ie, duration >6 months, pain NRS >4/10; low back and neck pain 89%, other 11%).[96] In addition to standard pain questionnaires, patients were assessed with a battery of cognitive tests to assess and monitor potential cognitive side effects.[96] The incidence of probable NP (ie, PDQ>18) declined with age. At pretreatment, NP could be diagnosed in 42% (13/31) of patients of 65 years or younger, in 35% (7/20) between 65 and 75 years, in 18% (6/34) between 75 and 85 years and 18% (2/11) in patients older than 85 years.[96] After 6 months of treatment (mean daily dose 267.6±122.1 mg/day), mean PDQ significantly declined in all age groups (Figure 2): from 16.9±4.9 to 7.2±3.3 below 65 years of age, from 14.6±7.3 to 7.2±3.2 between 65 and 75 years, from 11.8±5.3 to 6.5±3.2 and from 10.0±62 to 6.2±2.9 in patients 75 to 85 or older than 85 years of age, respectively (Bonferroni corrected ANOVA and *t* test; $P<0.01$, for 6 months vs pretreatment comparison in all age groups).[96] Although neuropsychological performances tended to decline with age, no further impairment was observed during treatment.[96]

Neurodegenerative diseases are also increasing in parallel with life expectancy extension and population aging.[23–29,95] Treatment guidelines and recommendations are focused on core cognitive and motor symptoms and do not include analgesics; as a consequence, pain is often underdiagnosed and undertreated also in these conditions.[95]

In Parkinson's disease (PD) pain is one of the most frequent non-motor symptoms throughout the disease course, sometimes preceding the clinical motor stage for years.[97] PD patients present prevalent nociceptive musculoskeletal pain due to muscle stiffness and arthritis but also pain with NP features.[98] Typical PD pathological changes are found early in the disease in brainstem noradrenergic nuclei of locus coeruleus which project to the spinal dorsal horns to modulate pain processing.[82] Dopaminergic therapeutic agents are only partially effective against this pain condition, and nonsteroidal anti-inflammatory drugs are considered only second-line treatment due to the associated risk of adverse cardiovascular, gastrointestinal and renal events, especially in the elderly.[98] Moreover, physicians are somehow reluctant to prescribe opioids to PD patients since they can worsen motor and non-motor symptoms, such as constipation, hallucinations, and daytime sleepiness.[42,99] Tapentadol has the potential to enhance the noradrenergic tone in PD.[39,40]
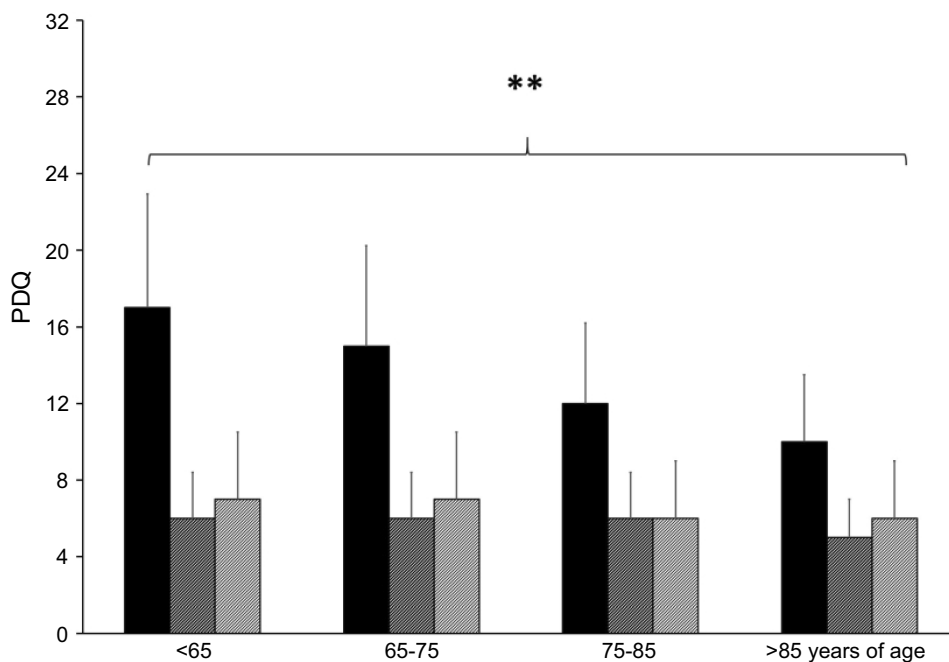
Figure 2 Means (± SD) of painDetect questionnaire score (PDQ) at pretreatment (solid columns) and after 3-month (densely hatched columns) and 6-month (lightly hatched columns) treatment with tapentadol for chronic musculoskeletal pain, across different age groups. **Different from baseline ($P<0.01$, 6-month PDQ vs pretreatment PDQ, for all age group; 1-way ANOVA and t-test).

In a retrospective study, Freo et al evaluated effects of a 6-month treatment with tapentadol in 21 PD patients (final mean daily doses 206.3±102.7).[100] Patients were assessed for the intensity of pain with 0–10 pain NRS and PDQ, for anxiety and depression with the Hospital Anxiety and Depression Scale, for cognitive and motor functions and for the quality of life with a set of neuropsychological tests.[100] At baseline, pain was classified as nociceptive, neuropathic and uncertain in eleven, three and seven patients (52, 14 and 33%, respectively).[100] NRS pain intensity decreased significantly over time (from 6.4±1.1 at baseline to 2.5±2.2 at month 6 of treatment, Bonferroni corrected ANOVA and t test, $P<0.0001$), with a final ≥50% pain relief in ten patients (48%).[100] From baseline to month 6 of treatment PDQ decreased from 11.4±4.5 to 5.1±4.9 ($P<0.0001$) (Figure 3); symptoms of anxiety and depression and the quality of life improved significantly. No decrement was observed in cognitive and motor functions.[100]

Conclusion

NP in general remains a challenging condition, and "traditional" analgesic therapies are known to often be poorly effective in this setting.

The pharmacological profile of tapentadol, combining synergistically MOR agonism and NRI in one molecule, appears to be unique and it seems reasonable to propose for tapentadol as the first, and so far only – molecule of a new class of central-acting analgesics, designated MOR-NRI.[101] For tapentadol the experimental evidence that NRI is a key mechanism that can be predominant in chronic neuropathic pain, reinforces the concept that tapentadol is different to classical opioids.[102] This concept has been strengthened by Raffa et al.[101] and Pergolizzi et al.[102] who stated that recognition of subclasses of opioids is warranted scientifically and beneficial to healthcare providers, payers and regulators; to date, some definitions have been proposed such as 'atypical' analgesic or multigesic agent.[101,102] To date, tapentadol PR, at full doses (300–450 mg/day) proved to be effective in the treatment of a challenging NP condition like DPN, and therefore may represent a suitable *a priori* choice for these conditions

So far, however, only preliminary evidence supports the use of this molecule in peripheral artery disease and PD. In any case, the inclusion of the NRI component reduces the "opioid load" and may thus mitigate side effects associated with opioid use – including those on cognitive function – in patients with these painful conditions, who are often poly-medicated and do require treatments with minimal potential of pharmacological interactions. Although – with the exception of DPN – robust randomized, placebo-controlled trials are missing for most other types of chronic NP, evidence from animal models
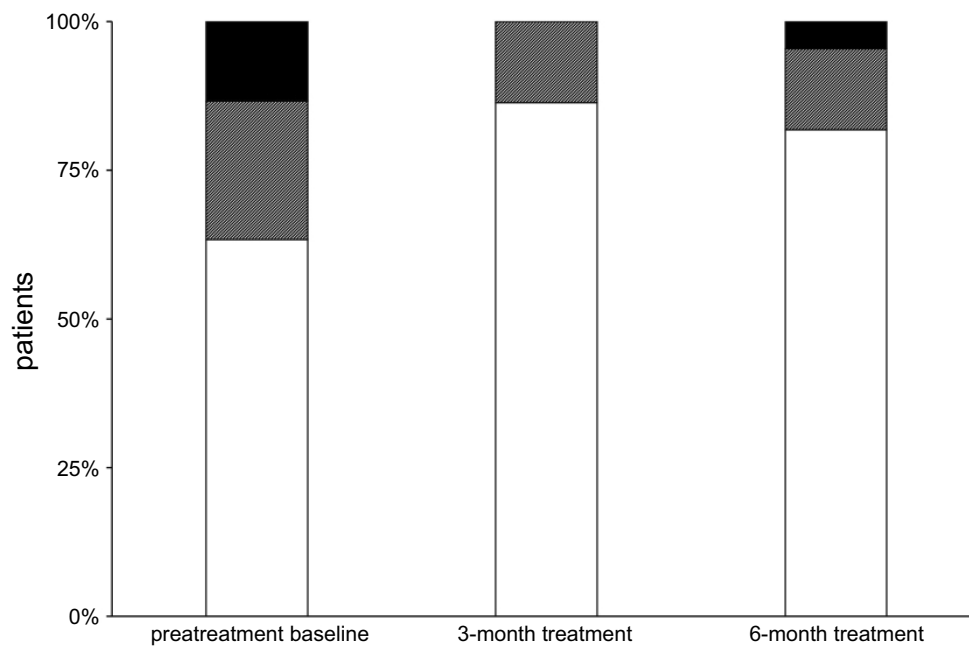
Figure 3 Parkinson's disease patients (percentage) who presented with nociceptive pain (open bars), mixed pain (hatched bars) and neuropathic pain (solid bars) at pretreatment baseline, and at follow-up assessment at month 3 and 6 of treatment with tapentadol.

suggests that NRI is a key mechanism and may even predominate over opioid actions in chronic (and especially neuropathic) pain states, reinforcing that tapentadol is different to classical opioids. Therefore, tapentadol PR should be a good choice for a tentative treatment of neuropathic and mixed pain, but there is still much room for further conclusive, high-quality clinical studies with this drug in NP syndromes.

Key points

- NP remains a challenging condition, not least because "traditional" analgesic therapies are often poorly effective.
- Tapentadol is characterized by a peculiar dual mechanism of action, namely the μ-opioid receptor agonism and norepinephrine reuptake inhibition.
- This dual mode of action indicates its potential suitability for a broad range of pain conditions, in particular whenever a NP component is present or cannot be excluded.
- Tapentadol is the first central-acting analgesic that has obtained a precise FDA recognition of specific and documented efficacy in the treatment of DPN.
- Tapentadol PR, at full doses (300–450 mg/day) proved to be effective in the treatment of a challenging condition, such as DPN. However, so far only preliminary evidence supports the use of this molecule for mixed pain in peripheral artery disease and PD patients.

- In any case, the NRI component reduces the "opioid load" and might thus mitigate common side effects associated with opioid use – including those on cognitive function.

Abbreviations list

ANCOVA and ANOVA, analysis of variance and of covariance; CINP, chemotherapy-induced neuropathy; CLBP, chronic low back pain; CNP, chronic neck pain; DPN, diabetic peripheral neuropathy DN4, Douleur Neuropathique en 4 Questions; EuroQol-5D, European Quality of Life-5 Dimensions; ITT, intention-to-treat; LANSS, Leeds Assessment of Neuropathic Symptoms; LOCF, last observation carried forward; MOR, mu opioid receptor agonist; NP, neuropathic pain; NPSI, Neuropathic Pain Symptom Inventory; NRI, norepinephrine reuptake inhibitor; PD, Parkinson's disease; PDQ, painDetect Questionnaire; PEA, palmitoylethanolamide; PHN, postherpetic neuralgia; PPN, painful peripheral neuropathies.

Acknowledgments

Disclosure

UF reports personal fees from Grunenthal, outside the submitted work; HGK has received speaker's and/or consultancy fees from Bionorica SE, Grunenthal GmbH, Mundipharma Int., TEVA ratiopharm, Mylan, and Pfizer outside the submitted work. HGK reports non-financial support from Grunenthal, during the conduct of the study; personal fees from Bionorica SE, Grunenthal GmbH, Mundipharma Int., TEA ratiopharm, Mylan, Pfizer, outside the submitted work. The authors report no other conflicts on interest in this work.

References

1. Treede RD, Jensen TS, Campbell JN, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. *Neurology.* 2008;70:1630–1635. doi:10.1212/01. wnl.0000282763.29778.59

2. Finnerup NB, Haroutounian S, Kamerman P, et al. Neuropathic pain: an updated grading system for research and clinical practice. *Pain.* 2016;157:1599–1606. doi:10.1097/j.pain.0000000000 0000492

3. Attal N, Bouhassira D, Baron R. Diagnosis and assessment of neuropathic pain through questionnaires. *Lancet Neurol.* 2018;17:456–466. doi:10.1016/S1474-4422(18)30071-1

4. Magrinelli F, Zanette G, Tamburin S. Neuropathic pain: diagnosis and treatment. *Pract Neurol.* 2013;13:292–307. doi:10.1136/pract-neurol-2013-000536

5. Attal N, Bouhassira D. Can pain be more or less neuropathic? *Pain.* 2004;110:510–511.

6. Bennett MI, Smith BH, Torrance N, Lee AJ. Can pain can be more or less neuropathic? Comparison of symptom assessment tools with ratings of certainty by clinicians. *Pain.* 2006;122:289–294. doi:10.1016/j.pain.2006.02.002

7. Bouhassira D, Attal N. The multiple challenges of neuropathic pain. *Neurosci Lett.* 2018;S0304–40. https://doi.org/10.1016/j.neu let.2018.11.054

8. Freynhagen R, Arevalo Parada H, Calderon-Ospina CA, et al. Current understanding of the mixed pain concept: a brief narrative review. *Curr Med Res Opin.* 2018;7:1–16.

9. Cruccu G, Finnerup NB, Jensen TS, et al. Trigeminal neuralgia: new classification and diagnostic grading for practice and research. *Neurology.* 2016;87:220–228. doi:10.1212/WNL.00000000 00002840

10. Smith BH, Torrance N. Epidemiology of neuropathic pain and its impact on quality of life. *Curr Pain Headache Rep.* 2012;16:191–198. doi:10.1007/s11916-012-0256-0

11. Bouhassira D, Lantéri-Minet M, Attal N, Laurent B, Touboul C. Prevalence of chronic pain with neuropathic characteristics in the general population. *Pain.* 2008;136:380–387. doi:10.1016/j. pain.2007.08.013

12. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* 2012;380:2163–2196. doi:10.1016/S0140-6736(12)61729-2

13. Moriarty O, Ruane N, O'Gorman D, et al. Cognitive impairment in patients with chronic neuropathic or radicular pain: an interaction of pain and age. *Front Behav Neurosci.* 2017;11:100. doi:10.3389/ fnbeh.2017.00246

14. Stocks J, Tang NK, Walsh DA, et al. Bidirectional association between disturbed sleep and neuropathic pain symptoms: a prospective cohort study in post-total joint replacement participants. *J Pain Res.* 2018;11:1087–1093. doi:10.2147/JPR.S149830

15. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol.* 2015;162–173. doi:10.1016/S1474-4422(14) 70251-0

16. Moore A, Derry S, Wiffen P. Gabapentin for chronic neuropathic pain. *JAMA.* 2018;319:818–819. doi:10.1001/jama.2017.21547

17. Langley PC, Van Litsenberg C, Cappelleri JC, Carroll D. The burden associated with neuropathic pain in western Europe. *J Med Econ.* 2013;16:85–95. doi:10.3111/13696998.2012.729548

18. Arendt-Nielsen L, Morlion B, Perrot S, et al. Assessment and manifestation of central sensitisation across different chronic pain conditions. *J Pain Eur.* 2018;22:216–241.

19. Mu A, Weinberg E, Moulin DE, Clarke H. Pharmacologic management of chronic neuropathic pain: review of the canadian pain society consensus statement. *Can Fam Physician.* 2017;63:844–852.

20. Tampin B, Briffa NK, Goucke R, Slater H. Identification of neuropathic pain inpatients with neck/upper limb pain: application of a grading system and screening tools. *Pain.* 2013;154:2813–2822. doi:10.1016/j.pain.2013.08.018

21. Hasvik E, Haugen AJ, Gjerstad J, Grøvle L. Assessing neuropathic pain in patients with low back-related leg pain: comparing the painDETECT questionnaire with the 2016 NeuPSIG grading system. *J Pain Eur J Pain.* 2018;22:1160–1169. doi:10.1002/ejp.1204

22. Chiò A, Mora G, Lauria G. Pain in amyotrophic lateral sclerosis. *Lancet Neurol.* 2017;16:144–157. doi:10.1016/S1474-4422(16) 30358-1

23. Ford B. Pain in Parkinson's disease. *Mov Disord.* 2010;25:S98–S103. doi:10.1002/mds.v25.1s

24. Buhmann C, Wrobel N, Grashorn W, et al. Pain in Parkinson disease: a cross-sectional survey of its prevalence, specifics,and therapy. *J Neurol.* 2017;264:758–769. doi:10.1007/s00415-017-8426-y

25. Scherder EJ, Plooij B. Assessment and management of pain, with particular emphasis on central neuropathic pain, in moderate to severe dementia. *Drugs Aging.* 2012;29:701–706. doi:10.1007/ s40266-012-0001-8

26. Reichling DB, Levine JD. Pain and death: neurodegenerative disease mechanisms in the nociceptor. *Ann Neurol.* 2011;69:13–21. doi:10.1002/ana.22351

27. Kurien T, Arendt-Nielsen L, Petersen KK, et al. Preoperative neuropathic pain like symptoms and central pain mechanisms in knee osteoarthritis predicts poor outcome 6 months after total knee replacement surgery. *J Pain.* 2018;19(11):1329–1341.

28. Thakur M, Dickenson AH, Baron R. Osteoarthritis pain: nociceptive or neuropathic? *Nat Rev Rheumatol.* 2014;10:374–380. doi:10.1038/nrrheum.2014.47

29. French HP, Smart KM, Doyle F. Prevalence of neuropathic pain in knee or hip osteoarthritis: a systematic review and meta-analysis. *Semin Arthritis Rheum.* 2017;47:1–8. doi:10.1016/j.semarthrit.2017.02.008

30. Ito S, Kobayashi D, Murasawa A, Narita I, Nakazono K. An analysis of the neuropathic pain components in rheumatoid arthritis patients. *Intern Med.* 2018;57:479–485. doi:10.2169/internalmedi-cine.9235-17

31. Sofat N, Harrison A, Russell MD, et al. The effect of pregabalin or duloxetine on arthritis pain: a clinical and mechanistic study in people with hand osteoarthritis. *J Pain Res J Pain Res.* 2017;10:2437–2449. doi:10.2147/JPR.S147640

32. Wang ZY, Shi SY, Li SJ, et al. Efficacy and safety of duloxetine on osteoarthritis knee pain: a meta-analysis of randomized controlled trials. *Pain Med.* 2015;16:1373–1385. doi:10.1111/ pme.12800

33. Gok K, Cengiz G, Erol K, Ozgocmen S. Neuropathic pain component in axial spondyloarthritis and the influence on disease burden. *J Clin Rheumatol*. 2018;24:324–327. doi:10.1097/RHU.0000000000000711

34. Moss P, Benson HAE, Will R, Wright A. Patients with knee osteoarthritis who score highly on the PainDETECT questionnaire present with multimodality hyperalgesia, increased pain, and impaired physical function. *Clin J Pain*. 2018;34:15–21. doi:10.1097/AJP.0000000000000504

35. Adewusi JK, Hadjivassiliou M, Vinagre-Aragón A, et al. Peripheral neuropathic pain in idiopathic Parkinson's disease: prevalence and impact on quality of life; a case controlled study. *J Neurol Sci*. 2018;392:3–7. doi:10.1016/j.jns.2018.06.022

36. American Geriatrics Society Panel on the Pharmacological Management of Persistent Pain in Older Persons. Pharmacological management of persistent pain in older persons. *J Am Ger Soc*. 2009;57:1331–1339. doi:10.1111/j.1532-5415.2009.02376.x

37. Kress HG. Tapentadol and its two mechanisms of action: is there a new pharmacological class of centrally-acting analgesics on the horizon? *Eur J Pain*. 2010;14:781–783. doi:10.1016/j.ejpain.2010.06.017

38. Kress HG, Koch ED, Kosturski H, et al. Direct conversion from tramadol to tapentadol prolonged release for moderate to severe, chronic malignant tumour-related pain. *Eur J Pain*. 2016;20:1513–1518. doi:10.1002/ejp.875

39. Tzschentke TM, Christoph T, Kögel B, et al. (-)-(1R,2R)-3-(3-dimethyl-lamino-1-ethyl-2-methyl-propyl)-phenol hydrochloride (tapentadol HCl): a novel mu-opioid receptor agonist/norepinephrine reuptake inhibitor with broad-spectrum analgesic properties. *J Pharmacol Exp Ther*. 2007;323:265–276. doi:10.1124/jpet.107.126052

40. Schukro RP, Oehmke MJ, Geroldinger A, Heinze G, Kress H-G, Pramhas S. Efficacy of duloxetine in chronic low back pain with a neuropathic component: a randomized, double-blind, placebo-controlled crossover trial. *Anesthesiology*. 2016;124:150–158. doi:10.1097/ALN.0000000000000902

41. Chang EJ, Choi EJ, Kim KH. Tapentadol: can it kill two birds with one stone without breaking windows? *Korean J Pain*. 2016;29 (3):153–157. doi:10.3344/kjp.2016.29.3.153

42. Langford RM, Knaggs R, Farquhar-Smith P, Dickenson AH. Is tapentadol different from classical opioids? A review of the evidence. *Br J Pain*. 2016;10:217–221. doi:10.1177/2049463716657363

43. Niesters M, Proto PL, Aarts L, Sarton EY, Drewes AM, Dahan A. Tapentadol potentiates descending pain inhibition in chronic pain patients with diabetic polyneuropathy. *Br J Anaesth*. 2014;113:148–156. doi:10.1093/bja/aeu056

44. Bortolotto V, Grilli M. Opiate analgesics as negative modulators of adult hippocampal neurogenesis: potential implications in clinical practice. *Front Pharmacol*. 2017;8:254. doi:10.3389/fphar.2017.00254

45. Kress HG, Ahlbeck K, Aldington D, et al. Managing chronic pain in elderly patients requires a CHANGE of approach. *Curr Med Res Opin*. 2014;30:1153–1164. doi:10.1185/03007995.2014.887005

46. Kress HG, Koch ED, Kosturski H, et al. Tapentadol prolonged release for managing moderate to severe, chronic malignant tumor-related pain. *Pain Physician*. 2014;17:329–343.

47. Pergolizzi J, Alon E, Baron R, et al. Tapentadol in the management of chronic low back pain: a novel approach to a complex condition? *J Pain Res*. 2011;4:203–210. doi:10.2147/JPR.S19625

48. Steigerwald I, Müller M, Davies A, et al. Effectiveness and safety of tapentadol prolonged release for severe, chronic low back pain with or without a neuropathic pain component: results of an open-label, phase 3b study. *Curr Med Res Opin*. 2012;28:911–936. doi:10.1185/03007995.2012.679254

49. Baron R, Eberhart L, Kern KU, et al. Tapentadol prolonged release for chronic pain: a review of clinical trials and 5 years of routine clinical practice data. *Pain Pract*. 2017;17:678–700. doi:10.1111/papr.12515

50. Horgas AL. Pain management in older adults. *Nurs Clin North Am*. 2017;52:e1–e7. doi:10.1016/j.cnur.2017.08.001

51. Afilalo M, Etropolski MS, Kuperwasser B, et al. Efficacy and safety of tapentadol extended release compared with oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee: a randomized, double-blind, placebo- and active-controlled phase III study. *Clin Drug Investig*. 2010;30:489–505.

52. Buynak R, Shapiro DY, Okamoto A, et al. Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomized, double-blind, placebo- and active-controlled phase III study. *Expert Opin Pharmacother*. 2010;11:1787–1804. doi:10.1517/14656566.2010.526106

53. Imanaka K, Tominaga Y, Etropolski M, et al. Efficacy and safety of oral tapentadol extended release in japanese and korean patients with moderate to severe, chronic malignant tumor-related pain. *Curr Med Res Opin*. 2013;29:1399–1409. doi:10.1185/03007995.2013.840568

54. Imanaka K, Tominaga Y, Etropolski M, Ohashi H, Hirose K, Matsumura T. Ready conversion of patients with well-controlled, moderate to severe, chronic malignant tumor-related pain on other opioids to tapentadol extended release. *Clin Drug Investig*. 2014;34:501–511. doi:10.1007/s40261-014-0204-3

55. England JD, Asbury AK. Peripheral neuropathy. *Lancet*. 2004;363:2151–2161. doi:10.1016/S0140-6736(04)16508-2

56. Dworkin RH, O'Connor AB, Audette J, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clin Proc*. 2010;853S:S3–S14. doi:10.4065/mcp.2009.0649

57. Schwartz S, Etropolski M, Shapiro DY, et al. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial. *Curr Med Res Opin*. 2011;27:151–162. doi:10.1185/03007995.2010.537589

58. Tominaga Y, Koga H, Uchida N, et al. Methodological issues in conducting pilot trials in chronic pain as randomized, double-blind, placebo-controlled studies. *Drug Res (Stuttg)*. 2016;66:363–370. doi:10.1055/s-0042-107669

59. Vinik A, Shapiro D, Rauschkolb C, et al. A randomized withdrawal, placebo-controlled study evaluating the efficacy and tolerability of tapentadol extended release in patients with chronic painful diabetic peripheral neuropathy. *Diabetes Care*. 2014;37:2302–2309. doi:10.2337/dc13-2291

60. Schwartz S, Etropolski MS, Shapiro DY, et al. A pooled analysis evaluating the efficacy and tolerability of tapentadol extended release for chronic, painful diabetic peripheral neuropathy. *Clin Drug Investig*. 2015;35:95–108. doi:10.1007/s40261-014-0249-3

61. Tedeschi A, De Bellis A, Francia PG, et al. Tapentadol prolonged pelease reduces the severe chronic ischaemic pain and improves the quality of life in patients with type 2 diabetes. *J Diabetes Res*. 2018;2018:1081792. doi:10.1155/2018/1081792

62. Galiè E, Villani V, Terrenato I, Pace A. Tapentadol in neuropathic pain cancer patients: a prospective open label study. *Neurol Sci*. 2017;38:1747–1752. doi:10.1007/s10072-017-3035-1

63. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med*. 2006;3:e442. doi:10.1371/journal.pmed.0030442

64. Johnson RW, Wasner G, Saddier P, Baron R. Postherpetic neuralgia: epidemiology, pathophysiology and management. *Expert Rev Neurother*. 2007;7:1581–1595. doi:10.1586/14737175.7.11.1581

65. Schmader KE. Epidemiology and impact on quality of life of postherpetic neuralgia and painful diabetic neuropathy. *Clin J Pain*. 2002;18:350–354.

66. Addington J, Freimer M. Chemotherapy-induced peripheral neuropathy: an update on the current understanding. *F1000Res*. 2016;5: F1000. doi:10.12688/f1000research

67. Dougherty PM. Is chemotherapy-induced peripheral neuropathy more than just a peripheral nervous system disorder? *Anesthesiology*. 2016;124:992–993. doi:10.1097/ALN.0000000000001085

68. Schreiber AK, Nones CF, Reis RC, Chichorro JG, Cunha JM. Diabetic neuropathic pain: physiopathology and treatment. *World J Diabetes*. 2015;6:432–444. doi:10.4239/wjd.v6.i3.432

69. Simón-Arceo K, González-Trujano ME, Coffeen U, et al. Neuropathic and inflammatory antinociceptive effects and electrocortical changes produced by *Salvia divinorum* in rats. *J Ethnopharmacol*. 2017;206:115–124. doi:10.1016/j.jep.2017.05.016

70. Selvarajah D, Wilkinson ID, Davies J, Gandhi R, Tesfaye S. Central nervous system involvement in diabetic neuropathy. *Curr Diab Rep*. 2011;11:310–322. doi:10.1007/s11892-011-0205-z

71. Ossipov MH, Morimura K, Porreca F. Descending pain modulation and chronification of pain. *Curr Opin Support Palliat Care*. 2014;8:143–151. doi:10.1097/SPC.0000000000000055

72. Velasco R, Bruna J. Taxane-induced peripheral neurotoxicity. *Toxics*. 2015;3:152–169. doi:10.3390/toxics3020152

73. O'Brien T, Christrup LL, Drewes AM, et al. European pain federation position paper on appropriate opioid use in chronic pain management. *Eur J Pain*. 2017;21:3–19. doi:10.1002/ejp.970

74. Bril V, England J, Franklin GM, et al. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology*. 2011;76:1758–1765. doi:10.1212/WNL.0b013e3182166ebe

75. Pergolizzi J, Böger RH, Budd K, et al. Opioids and the management of chronic severe pain in the elderly: consensus statement of an international expert panel with focus on the six clinically most often used World Health Organization step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). *Pain Pract*. 2008;8:287–313. doi:10.1111/j.1533-2500.2008.00204.x

76. Kern KU, Schwickert-Nieswandt M. Post-zoster-neuralgie des linken trigeminusastes V1 [Postherpetic neuralgia of the left trigeminus nerve V1: successful therapy with capsaicin 8% patch]. *Schmerz*. 2018;32:464–467. doi:10.1007/s00482-018-0333-3

77. Ylitalo KR, Sowers M, Heeringa S. Peripheral vascular disease and peripheral neuropathy in individuals with cardiometabolic clustering and obesity: national health and nutrition examination survey 2001-2004. *Diabetes Care*. 2011;34:1642–1647. doi:10.2337/dc10-2150

78. Freynhagen R, Baron R. The evaluation of neuropathic components in low back pain. *Curr Pain Headache R*. 2009;13:185–190. doi:10.1007/s11916-009-0032-y

79. Freynhagen R, Baron R, Gockel U, Tolle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Curr Med Res Opin*. 2006;22:1911–1920. doi:10.1185/030079906X132488

80. Fishbain DA, Cole B, Lewis JE, Gao J. What is the evidence that neuropathic pain is present in chronic low back pain and soft tissue syndromes? An evidence-based structured review. *Pain Med*. 2014;15:4–15. doi:10.1111/pme.12229

81. Liu R, Kurihara C, Tsai HT, et al. Classification and treatment of chronic neck pain: a longitudinal cohort study. *Reg Anesth Pain Med*. 2017;42:52–61; #. doi:10.1097/AAP.0000000000000505

82. Baron R, Kern U, Müller M, Dubois C, Falke D, Steigerwald I. Effectiveness and Tolerability of a moderate dose of tapentadol prolonged release for managing severe, chronic low back pain with a neuropathic component: an open-label continuation arm of a randomized phase 3b study. *Pain Pract*. 2015;15:471–486. doi:10.1111/papr.12199

83. Passavanti MB, Fiore M, Sansone P, et al. The beneficial use of ultramicronized palmitoylethanolamide as add-on therapy to Tapentadol in the treatment of low back pain: a pilot study comparing prospective and retrospective observational arms. *BMC Anesthesiol*. 2017;17:171. doi:10.1186/s12871-017-0461-9

84. Baron R, Jansen JP, Binder A, et al. Tolerability, safety, and quality of life with tapentadol prolonged release (PR) compared with oxycodone/naloxone PR in patients with severe chronic low back pain with a neuropathic component: a randomized, controlled, open-label, phase 3b/4 trial. *Pain Pract*. 2016;16:600–609. doi:10.1111/papr.12361

85. Ueberall MA, Mueller-Schwefe GH. Efficacy and tolerability balance of oxycodone/naloxone and tapentadol in chronic low back pain with a neuropathic component: a blinded end point analysis of randomly selected routine data from 12-week prospective open-label observations. *J Pain Res*. 2016;9:1001–1020. doi:10.2147/JPR.S112418

86. Duarte GS, Santos J, Costa J. Response to the publication by Ueberall and Mueller-Schwefe. *J Pain Res*. 2017;10:1055–1058. doi:10.2147/JPR.S135619

87. Baron R, Kennes LN, Elling C. Retrospective analyses versus RCTs: comparing like with like? *J Pain Res*. 2017;10:783–786. doi:10.2147/JPR.S133369

88. Billeci D, Coluzzi F. Tapentadol extended release for the management of chronic neck pain. *J Pain Res*. 2017;10:495–505. doi:10.2147/JPR.S129056

89. Matsuo Y, Kurata J, Sekiguchi M, Yoshida K, Nikaido T, Konno S-I. Attenuation of cortical activity triggering descending pain inhibition in chronic low back pain patients: a functional magnetic resonance imaging study. *J Anesth*. 2017;31:523–530. doi:10.1007/s00540-017-2343-1

90. Wu Q, Inman RD, Davis KD. Neuropathic pain in ankylosing spondylitis: a psychophysics and brain imaging study. *Arthritis Rheum*. 2013;65:1494–1503. doi:10.1002/art.37920

91. Fallon MT. Neuropathic pain in cancer. *Br J Anaesth*. 2013;111:105–111. doi:10.1093/bja/aet208

92. Coluzzi F, Raffa RB, Pergolizzi J, et al. Tapentadol prolonged release for patients with multiple myeloma suffering from moderate-to-severe cancer pain due to bone disease. *J Pain Res*. 2015;8:229–238. doi:10.2147/JPR.S83490

93. Brunetti GA, Palumbo G, Morano GS, et al. Tapentadol PR for pain syndromes in real life patients with hematological malignancy. *Cardiovasc Hematol Agents Med Chem*. 2016;14:68–74.

94. Nobile-Orazio E. Neuropathy and monoclonal gammopathy. In: Said G, Krarup C, editors. *Handbook of Clinical Neurology*. Vol. 115. (3rd series); Peripheral nerve disease. Amsterdam: Elsevier; 2013;443–459.

95. Chai E, Horton JR. Managing pain in the elderly population: pearls and pitfalls. *Curr Pain Headache Rep*. 2010;14:409–417. doi:10.1007/s11916-010-0148-0

96. Freo U. *Opiates and Cognitive Performances in the Fragile Patient*. Venice: XII Neuromodulation Meeting Abstract Book; 2018.

97. de Tommaso M, Arendt-Nielsen L, Defrin R, et al. Pain in neurodegenerative disease: current knowledge and future perspectives. *Behav Neurol*. 2016;2016:7576292.

98. Lin CH, Wu RM, Chang HY, et al. Preceding pain symptoms and Parkinson's disease: a nationwide populationbased cohort study. *Eur J Neurol*. 2013;20:1398e404. doi:10.1111/ene.12197

99. Brefel-Courbon C, Grolleau S, Thalamas C, et al. Comparison of chronic analgesic drugs prevalence in Parkinson's disease, other chronic diseases and the general population. *Pain*. 2009;141:14–18. doi:10.1016/j.pain.2008.04.026

100. Freo U, Furnari M, Ori C. Effects of tapentadol on pain, motor symptoms and cognitive functions in Parkinson's disease. *J Pain Res*. 2018;11:1849–1856. doi:10.2147/JPR.S164939

101. Raffa RB, Elling C, Tzschentke TM. Does 'strong analgesic' equal 'strong opioid'? Tapentadol and the concept of 'μ-load'. *Adv Ther*. 2018;35:1471–1484. doi:10.1007/s12325-018-0778-x

102. Pergolizzi JV Jr, LeQuang JA, Taylor R Jr, Ossipov MH, Colucci D, Raffa RB. Designing safer analgesics: a focus on μ-opioid receptor pathways. *Expert Opin Drug Discov*. 2018;13:965–972. doi:10.1080/17460441.2018.1511539

103. Sugiyama Y, Kataoka T, Tasaki Y, et al. Efficacy of tapentadol for first-line opioid-resistant neuropathic pain in Japan. *Jpn J Clin Oncol*. 2018;48(4):362–366.