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REVIEW

Where should analgesia lead to? Quality of life and functional recovery with tapentadol

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Abstract: Chronic pain is a major health-care problem worldwide, affecting more than one out of five adults in Europe. Although multiple analgesic agents have been extensively investigated in terms of clinical response and tolerability profile, few studies have focused on the impact of these therapies on patients' quality of life (QoL). Of note, improvement in QoL, together with functional recovery, has been recognized since the late 1990s as two main goals of analgesic therapy. Tapentadol is a novel analgesic molecule that synergistically combines two mechanisms of action, μ-opioid receptor agonism and norepinephrine reuptake inhibition, and for which multiple literature data are available that confirm its efficacy and safety in controlling pain. This narrative review summarizes the information available on the impact of tapentadol on QoL, with the aim to provide clinicians with a comprehensive overview of the analgesic effects of tapentadol prolonged release beyond the reduction of pain.

Keywords: pain, quality of life, tapentadol

Introduction

Chronic pain remains a major health-care problem worldwide, affecting more than one out of five adults in Europe.[1] Clinical outcomes of pain therapy, including reduction of pain and adverse event profiles, have been extensively investigated for a variety of analgesic agents.[2] However, the impact of different analgesic therapies on the quality of life (QoL) needs further investigation.[3–5] Improvement in QoL and functional recovery is to be considered the main goal of analgesic therapies, although this has been recognized since the late 1990s.[2,6] In this line, other outcomes, including functional recovery, maintenance of work productivity, and pharmacoeconomic considerations should be taken into account in the selection of analgesic therapy.[7]

Tapentadol is a dual μ-opioid receptor (MOR) agonist and noradrenaline reuptake inhibitor (NRI), considered as the first and unique member of a new class of analgesic agents, namely MOR-NRI.[8] The so-called "μ-load" of tapentadol is ≤40% relative to pure MOR agonists, thus resulting in a more favorable tolerability profile compared with strong opioids.[9] Moreover, tapentadol shows minimal serotoninergic activity, with long-term safety advantages (eg, reduced emesis).[10] The efficacy and safety of tapentadol, in its prolonged release (PR) formulation, have been evaluated in several pivotal trials and observational experiences, the presentation of which goes beyond the scopes of the present paper. Remarkably, tapentadol has been proposed to be different from classical opioids and may therefore represent an a priori choice for the treatment of chronic, neuropathic, and mixed pain.[11] This concept has been strengthened and expanded to other drugs – eg, tramadol,

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buprenorphine, loperamide, cebranopanol – since current evidence shows that the inclusion of all analgesics that share the opioid mechanism of action into the same class is anachronistic and misleading. The recognition of subclasses of opioids may be highly beneficial to health-care providers, payers and regulators; to date, some definitions have been proposed such as atypical or multigesic.[9,12]

The impact of tapentadol on the QoL has been investigated in several studies, also specifically conducted to address this issue. Moreover, evidence is available on functional recovery with tapentadol. This narrative, non-systematic review addresses the above, with the aim to provide clinicians with an overview of what "follows" the analgesic efficacy of tapentadol PR.

Tapentadol and QoL: available evidence

Several studies have comprised, among their outcomes, the evaluation of QoL in patients with chronic pain treated with tapentadol PR.

In our opinion, three different pooled analyses are specifically worth mentioning.[2,13,14] Moreover, another study specifically investigated QoL in patients treated with tapentadol.[15] We have decided to focus on these papers since they were specifically designed to investigate QoL in tapentadol-treated patients with pain of non-oncological etiology. Table 1 summarizes the main studies on this topic, as described below.

In 2010, Lange et al, performed a pooled analysis of data from three Phase III randomized studies in patients with chronic osteoarthritis of the knee or low back pain, which evaluated tapentadol PR (100–250 twice daily) compared with placebo or oxycodone controlled release (CR; 20–50 mg twice daily).[13] Data on QoL were collected using patient-reported outcomes, namely the patient global impression of change (PGIC), the Short Form-36 (SF-36) health survey,[16] and the EuroQol 5-Dimension (EQ-5D) health survey.[17] On the PGIC, patients rated their overall status on a scale from 1 to 7 (1=" very much improved" to 7=" very much worse"). The SF-36 evaluated patient health status in eight domains (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health) on a scale from 0 to 100 (0="poor health" to 100="good health") and two summary scales (the physical and mental component summaries). The EQ-5D health survey consisted of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) rated by patients on a 3-point scale (1="no problems", 2="some problems", 3="extreme problems"), an overall health state measure that was rated by patients on a 100 mm visual analog scale (VAS; 0="worst imaginable health state" to 100="best imaginable health state"), and a health status index, which calculated from the individual dimensions. On the PGIC, 56.7% treated with tapentadol PR (421/742) reported that their overall status was "much improved" or "very much improved" at endpoint, compared with 37.4% of patients in the placebo group (304/812) and 49.8% (310/622) of those in the oxycodone CR group. The advantage of tapentadol PR reached statistical significance compared with both controls ($p<0.001$). When the SF-36 questionnaire was evaluated, significant improvements from baseline to endpoint were observed with tapentadol PR compared with placebo in the physical functioning, role-physical, bodily pain and vitality scores ($p<0.05$ for all comparisons), and with oxycodone CR in all domains except general health. On the other hand, the results observed with oxycodone were similar, or even worse, to those reported with placebo. On the EQ-5D questionnaire, a greater improvement from baseline to endpoint was observed in the health status index score with tapentadol PR compared with placebo (LSMD vs placebo 0.0, 95% CI: 0.02–0.07; $p<0.001$), while the difference between oxycodone CR and placebo was not significant (−0.0, 95% CI: −0.02–0.02; $p=0.867$). A significantly greater improvement from baseline to endpoint in the health status index score was observed with tapentadol PR compared with oxycodone CR (LSMD between tapentadol PR and oxycodone CR −0.0, 95% CI: −0.07 to −0.02; $p<0.001$).

In 2016, Hofmann et al, performed a systematic comparison of three randomized trials on tapentadol PR and oxycodone CR in the treatment of chronic osteoarthritis pain (two studies) and severe low back pain (one study) using patient-relevant endpoints of efficacy, safety and health-related QoL (HRQoL).[2] In total, 2,968 patients were evaluated (tapentadol PR: 978, oxycodone CR: 999, placebo arms: 991). QoL was assessed by PCIG and EQ-5D, using sophisticated methods derived from health-technology assessment. Overall, statistical analysis showed superior treatment effects of tapentadol PR in HRQoL compared with oxycodone CR and placebo (Figure 1). In addition, given the more evident efficacy and more favorable safety of tapentadol PR over oxycodone shown in the same analysis, the investigators concluded that it may be beneficial to initiate treatment of

Table 1 Key elements from studies on the impact of tapentadol prolonged release on patients' quality of life in non-oncological patients

Study	Design	Patients enrolled	Tapentadol PR dosage	Duration study treatment	Impact on quality of life
Lange 2010[13]	Pooled analysis of three randomized, double-blind, active- (oxycodone CR 20–50 mg bid) and placebo-controlled phase III studies	2968 patients with moderate-to-severe OA-related knee pain or low back pain	Allowed dose range: 100–250 mg bid	3-week titration + 12-week maintenance	**PGIC score** Patients "much improved" or "very much improved" at endpoint Tapentadol PR: 56.7% ($p<0.001$ vs oxycodone and vs placebo) Oxycodone CR: 49.8% Placebo: 37.4% **SF-36 score** LSMD (95% CI) at endpoint vs baseline Tapentadol PR **vs placebo** Physical component: 1.9 (1.21, 2.65); $p<0.001$ Mental component: −0.6 (−1.34, 0.23); $p=0.167$ **Tapentadol PR vs oxycodone CR** Physical component: −1.3 (−2.06, −0.63); $p<0.001$ Mental component: −1.3 (−2.12, −0.56); $p<0.001$ **EQ-5D health status index** LSMD (95% CI) at endpoint vs baseline Tapentadol PR vs placebo: 0.0 (0.02–0.07); $p<0.001$ Tapentadol PR vs oxycodone CR: −0.0 (−0.07 to −0.02); $p<0.001$
Hoffman 2016[2]	Pooled analysis of three randomized, double-blind, multicenter, active- (oxycodone CR 20–50 mg bid) and placebo-controlled studies	2968 patients with chronic OA-related knee pain (two studies) or severe low-back pain (one study)	Allowed dose range: 100–250 mg bid	3-week titration + 12-week maintenance	**HRQoL** Relative risk for tapentadol PR vs oxycodone CR: 0.78 (95% CI 0.64–0.96); $p=0.02$
Lange 2017[14]	Pooled analysis of two randomized, double-blind, active- (oxycodone CR 20–50 mg bid) and placebo-controlled studies	2010 patients (≥40 years) with moderate-to-severe chronic OA-related knee pain	TTD: 300 mg Allowed dose range: 100–250 mg bid	3 week titration + 12 week maintenance	**PGIC score** Patients "much improved" or "very much improved" at endpoint Tapentadol PR: 57.3% ($p<0.001$ vs oxy and vs placebo) Oxycodone CR: 44.7% Placebo: 39.5% **SF-36 score** LSMD (95% CI) at endpoint vs baseline Tapentadol PR vs placebo Physical component: 1.78 (0.92–2.64); $p<0.001$ Mental component: −0.86 (−1.83–0.10); $p=0.78$ Tapentadol PR oxycodone CR: Physical component: 1.99 (1.13–2.85); $p<0.001$ Mental component: 1.60 (0.64–2.56); $p=0.01$ **EQ-5D health status index** LSMD (95% CI) at endpoint vs baseline Tapentadol PR vs placebo: 0.04 (0.02–0.07); $p=0.002$ Tapentadol PR vs oxycodone CR: 0.07 (0.04–0.09); $p<0.001$

(*Continued*)

Table 1 (Continued).

Study	Design	Patients enrolled	Tapentadol PR dosage	Duration study treatment	Impact on quality of life
Baron 2016[15]	Randomized, open-label, active-(oxycodone/naloxone PR 10 mg/5 mg – 40 mg/20 mg bid) controlled, phase IIIb–IV study	254 opioid-naïve patients with severe chronic low back pain with a neuropathic component	Allowed dose range: 50–250 mg bid	3-week titration + 9-week maintenance	**SF-12 score** Mean change (LS mean) at endpoint vs baseline for tapentadol PR Physical component: 9.74 (0.795); $p<0.001$ vs baseline, $p\leq0.017$ vs oxycodone/naloxone PR Mental component: 3.08 (0.846); $p<0.001$ vs baseline **EQ-5D health status index** Mean change (LS mean) at endpoint vs baseline for tapentadol PR 0.34 (0.028); $p<0.001$ vs baseline, $p=0.010$ superiority vs oxycodone/naloxone PR **HADS** Mean change (LS mean) at endpoint vs baseline for tapentadol PR Anxiety score: −2.1 (0.34); $p<0.001$ vs baseline, $p=0.032$ superiority vs oxycodone/naloxone PR Depression score: −2.4 (0.34); $p<0.001$ vs baseline, $p=0.011$ superiority vs oxycodone/naloxone PR

Abbreviations: CR, controlled release; PGIC, patient global impression of change; SF-36, Short Form-36; SF-12, Short Form-12; EQ-5D, EuroQol 5-Dimension; LSMD, least square mean difference; HADS, Hospital Anxiety and Depression Scale; HRQoL, Health-related quality of life; PR, prolonged release; OA, osteoarthritis.

chronic severe nonmalignant pain with tapentadol PR rather than oxycodone.

These findings were corroborated by those of another pooled analysis of two double-blind, randomized, placebo- and oxycodone CR-controlled studies in patients with moderate-to-severe chronic osteoarthritis knee pain.[14] In total, 2010 patients were evaluated. At analysis of PGIC, more patients in the tapentadol PR group (57.3%) compared with oxycodone CR (44.7%) and placebo patients (39.5%) rated their overall health status at the end of treatment as "very much improved" or "much improved" ($p<0.001$ for tapentadol PR vs both oxycodone and placebo; no differences between oxycodone and placebo were reported).[14] A significant advantage was also observed for tapentadol PR over oxycodone CR in terms of physical and mental SF-36 dimensions, while the mental component score significantly worsened with oxycodone treatment when compared with placebo. Increases in the weighted EQ-5D health status compared with baseline were reported in all groups but were highest for tapentadol PR (LS mean=0.04 [95% CI: 0.02–0.07] vs placebo and =0.07 [95% CI: 0.04–0.09]; $p<0.001$ vs oxycodone). The comparison between oxycodone and placebo was significantly in favor of placebo.

In a randomized, controlled, open-label, Phase IIIb/IV trial, Baron et al, evaluated the QoL in opioid-naive patients with severe chronic low back pain with a neuropathic component treated with tapentadol PR (n=129) or oxycodone/naloxone PR (n=125) (Figure 2).[15] QoL was assessed by the SF-12 and the EQ-5D questionnaires. Moreover, the Hospital Anxiety and Depression Scale (HADS) was used to evaluate symptoms of anxiety and depression.[18] After 12-week treatment, significant improvements versus baseline were observed in the SF-12 total score and in all subdomains ($p<0.001$ vs baseline); in the oxycodone/naloxone PR group, significant improvements were observed only in the mean SF-12 physical component summary score and 7 SF-12 domain scores (all $p\leq0.012$). Remarkably, significantly greater improvements from baseline to final evaluation were observed in the tapentadol PR group compared with the oxycodone/naloxone PR group for the mean physical component summary score and six domain scores (all $p\leq0.017$). In addition, the EQ-5D health status improved in both groups, with a significant advantage for tapentadol over oxycodone/naloxone ($p=0.010$). Significant decreases from baseline to final evaluation were observed in the mean HADS anxiety and depression subscale scores in both treatment groups, with an advantage for tapentadol ($p=0.032$). These improvements in QoL were paralleled by an improvement in

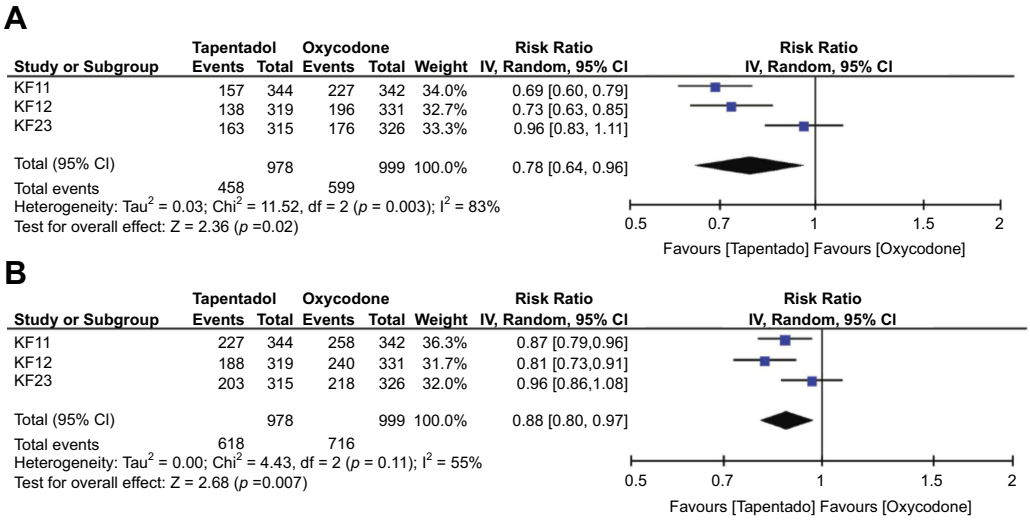

Figure 1 Meta-analysis of treatment effects for the EQ-5D comparing tapentadol PR versus oxycodone CR (ITT population). (**A**) Responders were defined using the anchor-based minimal important difference (MID) (0.036). (**B**) Responders were defined using a distribution-based MID (0.154). Copyright © 2016. Prime National Publishing Corp. Reproduced from Hofmann JF, Lal A, Steffens M, Boettger R. Patient-relevant outcomes and health-related quality of life in patients with chronic, severe, noncancer pain treated with tapentadol prolonged release-using criteria of health technology assessment. *J Opioid Manag*. 2016;12(5):323–331.[2]

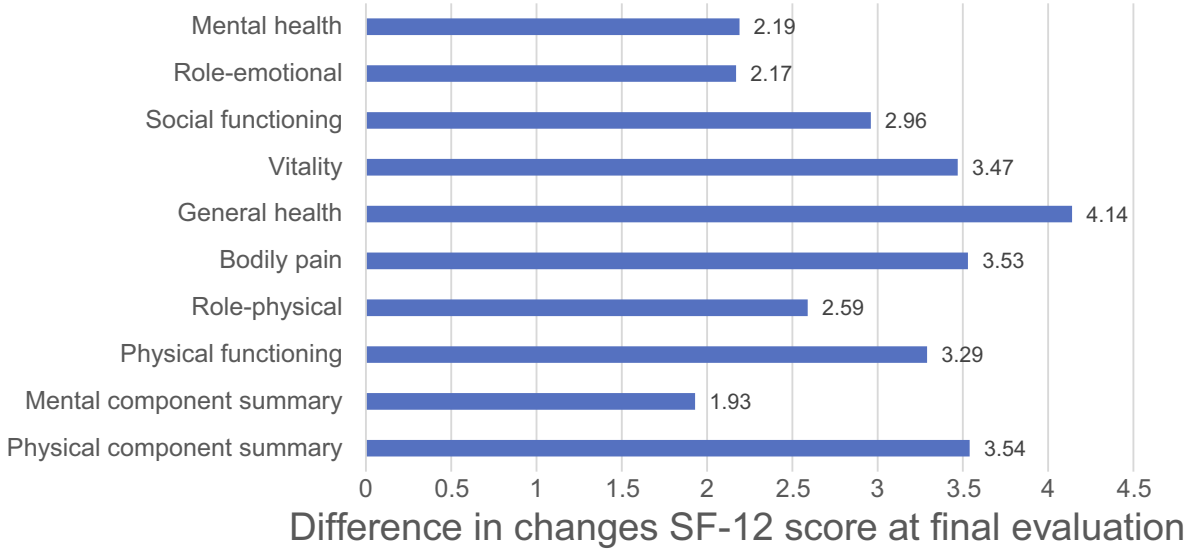

Figure 2 Difference in changes in SF-12 score at final evaluation, as compared with baseline, in patients treated with either tapentadol PR (N=129) or oxycodone/naloxone PR (N=125). Difference is expressed as change in the tapentadol group (final evaluation-baseline)-change in the oxycodone/naloxone group. Data from Baron et al.[15]

sleep quality: overall sleep quality was judged to be improved from baseline to final evaluation in 50.0% of patients in the tapentadol PR group and 37.7% of patients in the oxycodone/naloxone PR group.

Tapentadol and functional recovery

In the pooled analysis by Lange et al, which evaluated two double-blind, placebo- and oxycodone CR-controlled studies in patients with chronic osteoarthritis of the knee,[15] pain, disability, and joint stiffness were assessed by the WOMAC questionnaire (Likert scale from 0 to 4 lower scores indicate lower levels of symptoms).[19] Overall, there were no significant differences in mean changes from baseline to week 12 of the maintenance period in the WOMAC sub-scales and global scores between tapentadol PR and oxycodone CR (pain: −0.01, 95% CI: −0.13–0.12; physical functioning: −0.01, 95% CI: −0.13–0.12; stiffness: −0.05, 95% CI: −0.19–0.09; global score: 0.0, 95% CI: −0.12–0.12). However, tapentadol PR was significantly more effective than placebo in all four WOMAC scales, whereas a significant advantage for oxycodone versus placebo could not be shown for stiffness and the global WOMAC score.

Implications for clinical practice

Pain reduction remains the immediate outcome of analgesic therapy. However, in the last 20 years, mounting attention has been given to outcomes that go beyond the reduction of pain intensity, namely QoL and functional recovery. Indeed, a patient with reduced pain will likely experience an improvement of QoL and a recovery of the function of the affected area(s) in the case of musculoskeletal pain. Improved QoL and functionality will also turn into increased productivity of the patient – thus, further contributing to better QoL, in a vicious circle – and reduced need of other medical therapies, with a potential beneficial impact on the healthcare system. These improvements, however, may become less evident for some analgesic therapies, due to lack of efficacy or the onset of drug-associated adverse events.

Remarkably, despite its importance, the impact of different analgesic therapies on QoL and functional recovery has been poorly assessed to date,[3–5] whereas these evaluations may greatly help clinicians in the selection of treatment.

The impact of tapentadol PR on QoL and functional recovery have been assessed in pooled analyses of randomized trials of non-oncological pain with oxycodone CR as a comparator. Overall, these well-grounded pieces of evidence consistently show that therapy with tapentadol PR does improve all dimensions of QoL, often with a significant advantage over oxycodone. Enhanced QoL is associated with more evident functional recovery and improved sleep quality. This beneficial action of tapentadol PR can likely be due to its peculiar pharmacological action, which is characterized also by a marked noradrenergic activity. Further studies on this topic are, however, also warranted in other settings. For instance, an explorative study in patients with cancer pain showed improvement of QoL with tapentadol PR,[20] and additional evidence in this specific setting would be welcomed.

Some preliminary studies have also assessed whether the impact of tapentadol PR on QoL translates into improved productivity. In addition, a Bayesian Markov chain analysis showed that tapentadol was associated with less time missed from work, less impairment while working, and a lower overall loss in work productivity compared with oxycodone CR.[21] In a pharmacoeconomy analysis, tapentadol PR showed more favorable results over oxycodone/naloxone, since in 65% of cases it was less costly and produced a considerable quality-adjusted life years gain.[22] This more favorable cost-effectiveness was likely due to the price and the lower incidence of adverse events and related discontinuation rate, thus leading to a further economic advantage.

In conclusion, we believe that QoL and functional recovery should be better investigated in clinical trials on analgesic therapy. While results of dedicated studies appear awaited, current evidence specifically collected on tapentadol PR unequivocally shows its beneficial effect on QoL and functionality, thus contributing to a comprehensive recovery of the patient, and not only to pain reduction.

Key points

- Different analgesic therapies provide a reduction of pain and a good safety profile in the treatment of chronic pain, a condition that still represents a major health-care problem worldwide.
- In the last decades, quality of life (QoL) and functional recovery have emerged as two important goals of analgesic therapy; however, only few studies have investigated these aspects.
- Some pooled analyses have assessed the impact of tapentadol prolonged release (PR), a novel analgesic molecule acting on both μ-opioid receptor (MOR) agonism and norepinephrine reuptake inhibition (NRI), on QoL and functional recovery in patients with chronic pain related to knee osteoarthritis or low back pain.
- Literature data consistently show that tapentadol PR is associated with improvements in all dimensions of QoL (with superior results if compared with oxycodone CR), which in turns exerts a positive effect on functional recovery and sleep quality.
- Based on preliminary studies, tapentadol PR may have a positive impact also on patient's productivity.

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