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Pain reduction induced by tapentadol in patients with musculoskeletal chronic pain fosters better sleep quality

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Abstract

Background: Poor sleep may predict the increase and intensification of pain over time with increased insomnia symptoms being both a predictor and an indicator of worse pain outcomes and physical functioning status over time. However, the impact of different analgesic therapies on quality of life, functional recovery and sleep has been poorly assessed to date, whereas these evaluations may greatly help clinicians in the selection of treatment when dealing with patients with chronic pain (CP).

Methods: To explore whether tapentadol-induced pain relief may drive improved sleep quality, we carried out a pooled analysis of real-world data collected from 487 patients with CP (mean age, 68.3 years; 57.7% women) suffering from a wide range of chronic musculoskeletal pain conditions and treated with tapentadol.

Results: Following tapentadol treatment, patients experienced an 80% reduction in the frequency of very disturbed sleep as well as a 50% reduction in the predominant sleep complaint reported by patients with CP – that is, nocturnal awakenings. A significantly greater proportion of patients reported good/restful sleep at the end of the study period compared to baseline (72.4% *versus* 25.3%; $p<0.01$). This benefit was observed regardless of the clinical setting, treatment duration, posology or patient age and was associated with a higher proportion of patients reporting an improved global health status and good tolerability.

Conclusion: The reduction in pain intensity provided by tapentadol fosters sleep quality and favours a better quality of life. Therefore, our findings provide the rationale for addressing sleep quality as a relevant outcome, complementary to pain relief in CP management.

Keywords: chronic pain, functional recovery, sleep quality, tapentadol.

Citation

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Introduction

Chronic pain (CP) is a global health priority and, in primary care, is ranked as the leading cause of quality-adjusted life year loss, overriding coronary artery disease, hypertension, mood and anxiety disorders, diabetes, and common respiratory conditions.[1,2] A European survey in 2006 found that CP of moderate-to-severe intensity occurs in 19% of adults, seriously affecting the quality of their social and working lives;[3] a further cross-sectional study carried out in Italy in 2014 reported that CP prevalence was 28.4%.[4] CP is a major source of suffering, interferes with daily functioning (from concentrating on a task, to walking, sleeping, maintaining social relationships and holding down a job for independent living), often accompanied by distress, thus leading to disability and a significant burden on both individuals and society as a whole.[5] Of note, the remarkable societal burden associated with CP stems not only from healthcare costs but also from lost productivity as a result of the disability that pain produces.[6]

Accounting for almost one in four patients with CP worldwide, chronic low back pain (CLBP) is the most prevalent CP condition[7] and the leading global cause of years lived with disability.[2] To date, years lived with disability caused by CLBP have increased by more than 50% since 1990, especially in low-income and middle-income countries,[8] which will likely face greater challenges compared to high-income countries in managing the impact of the growing LBP burden in the near future.[2] Furthermore, in the context of musculoskeletal disorders, CP also affects more than one-third of patients with either hip or knee osteoarthritis (OA) and nearly 50% if OA is present in both joints,[9] thus considerably increasing the number

of people dealing with CP on a daily basis and deserving both adequate pain relief and effective functional recovery.

Over the past years, pain has been well recognized as a psychosocial issue posing a substantial burden on patients' quality of life (QoL)[10] and, in line with this, CP has recently been presented as a single disease entity the severity of which is best depicted through a multidimensional framework, including intensity of pain, pain-related distress and interference with daily living.[5] Thus, to fully acknowledge the multidimensional nature of pain, pain management should aim not only at achieving adequate pain relief but also at fully restoring patients' functionality in terms of psychological and physical well-being. In line with the evolving notion of pain as a biopsychosocial issue, functionality can be redefined as the ability to ambulate, maintain cognitive function, return to work and complete activities of daily living as well as the absence of mood and sleep disturbances. Such a definition acknowledges the bidirectional association between CP and sleep disturbances,[1,6,9,11] thus suggesting sleep quality as a clinically relevant target of analgesic therapy. However, the impact of different analgesic therapies on QoL and functional recovery has been poorly assessed to date, whereas these evaluations may provide guidance and greatly assist clinicians in the selection of treatment for patients with CP.

Tapentadol is an atypical opioid with two mechanisms of action, namely μ-opioid receptor (MOR) agonism and norepinephrine reuptake inhibition, that was found effective in patients who suffered from OA and LBP of moderate-to-severe intensity, showing similar efficacy but better gastrointestinal tolerability than oxycodone and therefore representing a good treatment option for CP management.[12–14] To explore whether tapentadol-induced pain relief may drive improved sleep quality, we carried out a pooled analysis of real-world data collected from patients suffering from a wide range of chronic musculoskeletal pain conditions and treated with tapentadol. Thus, our final aim relies on reaffirming the clinical relevance of targeting functional recovery and quality of sleep in patients with CP and showing how pain reduction, due to the tapentadol effect, fosters better sleep quality.

Beyond analgesia: functional recovery and improved sleep quality as therapeutic goals in CP management

During the past decades, limited attention has been given to outcomes that go beyond the reduction of pain intensity, namely QoL and functional recovery,[15] the improvement of which should be regarded as a main goal of analgesic therapy. However, a greater appreciation of the multidimensional nature of pain demands therapeutic approaches aimed at restoring the functionality of patients. From this new perspective, pain control should be regarded as the initial step in CP management as it may impede the progression of pain to impaired QoL, disability and, ultimately, morbidity. As full pain relief is not always achievable in patients with CP, other objectives, such as return to function, maintenance of work productivity and relevant biopsychosocial domains, including sleep quality, mental and physical health, and an overall sense of well-being, must be addressed as being of great value for patients.[16] In addition, a recent exploratory study has shown that patients judge certain specific QoL-related domains, such as improved sleep quality, reduced rescue medication intake and 'return to function' (e.g. the ability to perform meaningful activities by themselves), as the most valued outcomes.[16]

The concept of functionality has been a matter of discussion for a long time, and a recent survey unveiled that this concept has been used with different meaning by specialists and ranging from physical mobility and autonomy to comprehensive physical, social and psychological well-being. In this context, defining functionality as the ability to ambulate, to maintain cognitive function, to return to work and to complete activities of daily living is in complete harmony with the WHO definition of health as a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.[17]

Sleep is an essential aspect of health and regulates growth, development, immunity and metabolic functions. A mounting body of evidence suggests that sleep disturbance predisposes to or worsens any pain condition, with potential increases in central pain sensitivity.[9] Furthermore, poor sleep plays an important role in predicting the growth and intensification of pain over time,[18] with increased insomnia symptoms being both a predictor and an indicator of worse pain outcomes and physical functioning status over time.[1]

Sleep disturbances are commonly experienced by CP patients and are closely related to health-related QoL. Sleep disorders may augment stress levels, thus making it difficult for patients to perform simple tasks, as well as impairing their cognitive ability, in turn affecting daily living.[6] A bidirectional association between sleep and pain was also documented, whereby one night of poor sleep was followed by an increase in pain intensity the following day. Likewise, one day of greater pain intensity was followed by one night with sleep disturbances.[6] Whilst the neurobiology of sleep disturbance in CP displays overlapping features with the neurobiology of depression and sleep, there is evidence supporting the presence of a neurobiological link between pain and sleep, including the contribution of neurotransmitters, such as serotonin, norepinephrine, acetylcholine and endorphins, which may be involved in the regulation of pain, sleep and affect.[19] To date, insomnia is associated with low physical activity,[20,21] and it has been found that physical activity can also be a deterrent against the risk of back pain.[22]

Almost 50% of people with CLBP have sleeping disturbances, with an 18-fold increase in insomnia *versus* healthy people, and are more likely to experience other psychological disturbances.[23,24] Indeed, one of the comorbid problems with back pain is insomnia. A recent study investigated the relationship between sleep disturbances and back pain and

found that it is two sided – with sleep disturbance being associated with risk of back pain whilst back pain can also lead to sleep disturbances.[22] Thus, it can be hypothesized that, by reducing pain and physical dysfunction, sleep quality could be improved, thus enriching the QoL of people with CLBP. Similarly, improvements in sleep after cognitive behavioural therapy in patients with CP due to OA were associated with reduced pain.[25]

Nevertheless, many questions remain about the direction of causality in the sleep–pain association as well as about the mechanisms that may account for their association.[18] Although there is much evidence to support the finding that pain relief with opioid analgesics is associated with improved subjective reports of sleep, objective sleep improvement in patients with CP treated with opioid analgesics has not been as extensively studied. One critical question is whether a reduction in pain intensity following opioid therapy can foster better sleep quality. In other words, is there evidence to support the common clinical assumption that – on the positive side of the equation – pain relief achieved with opioid therapy should bring about an overall improvement in sleep quality? It is well known that pain is an unwelcome sleep partner. Pain tends to erode sleep quality and alter the sleep restorative process in vulnerable patients. It can contribute to next-day sleepiness and fatigue, affecting cognitive function. Pain and sleep management strategies should be personalized to reflect the patient's history and ongoing complaints.[26] Whether such an improvement may be accompanied by an increase in excessive daytime sleepiness and other undesirable side effects could not be excluded as somnolence, sedation, drowsiness and sleepiness were the most frequently reported sleep-related adverse events, thus reinforcing the importance for clinicians to effectively discriminate the observed benefit on sleep quality from the somnolence that opioids may induce in patients with CP.

Collectively, there is a great need to increase awareness on the contribution of sleep quality to the comprehensive functionality-driven framework and to gain better knowledge of how each analgesic drug may improve sleep quality as a result of pain intensity reduction. Such information should be included amongst those considered for selecting analgesic medications in CP management. Therefore, the evaluation of sleep quality should be included amongst the secondary outcomes of clinical studies assessing pain treatment options.[15] In this scenario, it would be important to explore whether tapentadol-induced pain relief may drive improved sleep quality with the limited occurrence of somnolence.

Real-life evidence of the impact of tapentadol on sleep quality in patients with CP: insights from a pooled analysis of observational studies

Tapentadol is a dual MOR agonist and noradrenaline reuptake inhibitor (NRI), considered as the first and unique member of a new class of analgesic agents, namely MOR–NRIs.[12,13] By virtue of the broad effectiveness of tapentadol for nociceptive, neuropathic and mixed pain, due to its unique combination of MOR and NRI activity,[12] tapentadol holds promise to simplify CP treatment by eliminating the need to isolate and treat the individual types of CP with a combination of different analgesics.[12] Earlier evidence suggested that, following tapentadol prolonged-release treatment, the improvements in QoL were paralleled by an amelioration in sleep quality in a greater proportion of patients compared to that of patients following oxycodone/naloxone prolonged-release treatment (50% *versus* 37.7%).[27,28] Subsequent studies in a real-life setting documented, along with effective pain control, similar improvements in mental and physical health and suggested beneficial effects in terms of less night awakenings and greater percentages of patients reporting restful sleep following tapentadol treatment.[29–31] Given the real-world evidence supporting tapentadol analgesic efficacy across a wide range of CP conditions,[29–36] we seek to evaluate its potential impact on sleep quality.

Methods

We pooled data from eight real-world studies including 487 patients with CP (mean age, 68.3 years; 57.7% women) who received treatment with tapentadol for different painful conditions, including LBP, neck pain and pain after knee replacement (Table 1).[29–36] All studies were open-label; four were prospective and two were retrospective studies. The eligibility criteria for inclusion in the present pooled analysis were the concomitant provision of subjective sleep assessment and pain intensity assessment in the same patient cohort. The primary endpoint in all studies was the change from baseline in pain intensity. Comparisons between baseline values and last post-treatment values were performed using the paired Student *t*-test for continuous parameters (SF12 questionnaire, physical and mental health functioning) and the nonparametric McNemar test for discrete parameters (quality of sleep). Differences were considered as statistically significant for values of $p<0.05$. With regards to the baseline characteristics of the pooled patient population prior to tapentadol treatment, pain levels (assessed by a numerical rating scale; NRS) were at ~7 and a mixed type of pain was predominant (65.6%; in cases where the type of pain was identified ($n=93$)). Patients were treated with tapentadol with treatment periods ranging from 21 days[29] to 6 months.[30,31] At the end of the study period, the dosing levels of tapentadol in the pooled patient population were 211.5 mg/die. Further information on the pain profile of patients and tapentadol treatment regimen of the individual studies included in the pooled analysis are provided in Table 2.

Results

Regardless of the clinical setting, treatment duration, posology or patient age, tapentadol was effective in significantly reducing mean pain intensity, as measured by NRS, from

Table 1. Studies included in the pooled analysis.

Study	Study design and patients	Tapentadol treatment duration	Primary endpoint and results	Secondary endpoints
Panella et al.[29] (2016)	Open-label, retrospective study in 144 patients in rehabilitation after knee replacement surgery with moderate-to-severe pain	Tapentadol PR (*n*=91) or paracetamol (*n*=53) for 21 days	Pain intensity assessed on NRS from 0 to 10 NRS baseline to end of treatment: –4.3 points	Sleep quality (measured on a 4-point scale (4, restorative; 3, good; 2, with frequent awakenings; 1, very disturbed)); functional recovery through range of motion (active and passive); muscle tone; Barthel index; comorbidities (CIRS scale) and resilience, i.e. the capacity of an individual to face stressful events and overcome them
Notaro[30] (2017)	Prospective, observational single-centre, 6-month study in 27 patients with chronic severe low back pain	Tapentadol PR for 180 days	Intensity of pain, assessed by a 11-point NRS (0–11) Δ NRS baseline to end of treatment: –3.7 points	Overall evaluation of efficacy and tolerability; nature of pain (PD-Q final score ≥19: neuropathic pain; 13–18: uncertain nature; ≤12: nociceptive pain); sleep quality, according to a 4-point scale; health status and QoL
Aurilio[32] (2019)	Investigator-driven, prospective, open-label, observational study in 20 patients naive to opioids and with persistent moderate-to-severe chronic pain	Tapentadol PR for 90 days	Proportion of responder patients, defined as patients who experienced a ≥30% reduction in pain intensity NRS baseline to end of treatment: –3.9 points	Pain intensity on the NRS both at rest and during loading; the quality of sleep (assessed on a subjective verbal scale with 4 points, where 0, very disturbed sleep; 1, frequent awakenings; 2, good sleep; 3, restful sleep); cognitive impairment; patient autonomy in both basic and instrumental activities of daily life, the presence of neuropathic pain
Orfei et al.[33] (2019)	Prospective, open-label, observational study in 25 adult patients with chronic pain	Tapentadol PR for 40 days	Proportion of responder patients, with ≥30% reduction in pain intensity NRS baseline to end of treatment: –4.8 points	Any change in pain intensity both at rest and during loading on the NRS score; the presence of the neuropathic component of pain; improvements in quality of daily life; the degree of disability; subjective therapy effectiveness; sleep quality on a 4-point scale (1, very disturbed; 2, with frequent awakenings; 3, good; 4, restful sleep); tolerability of tapentadol PR and the incidence of adverse events and treatment discontinuation
Billeci et al.[34] (2017)	Observational study in 54 patients with moderate-to-severe chronic neck pain	Tapentadol ER for 90 days	Change in average pain intensity from baseline (week 0) to week 12 NRS baseline to end of treatment: –5.1 points	Changes in neuropathic pain symptoms; QoL; pain-associated sleep interference (assessed on a 11-point NRS scale ranging from 0 (pain does not interfere with sleep) to 10 (pain completely interferes with sleep)); global impression of change; neck-specific disability and neck range of motion; adverse effects

(Continued)

Table 1. (*Continued*)

Study	Study design and patients	Tapentadol treatment duration	Primary endpoint and results	Secondary endpoints
Freo et al.[35] (2020)	Observational retrospective study in 65 young patients and 87 elderly patients with severe chronic low back pain	Tapentadol ER for 120 days	Changes from baseline in 24-h pain intensity on a 0–10 NRS at month 4 of treatment (titration plus maintenance periods) NRS baseline to end of treatment: –5.3 points (young); –4.8 points (elderly)	Neuropathic pain intensity; QoL and sleep; and cognitive and gastrointestinal functions
Oriente[31] (2020)	Prospective, open-label, single-centre, observational study in 35 patients with pain after vertebral fracture due to bone fragility	Tapentadol PR for 180 days	30% intensity reduction of the load-related and movement-related pain from baseline to end of the study using the 0–10 NRS NRS baseline to end of treatment: –4.07 points	50% intensity reduction of the load-related and movement-related pain from baseline to end of the study; sleep quality measured by 4-point subjective verbal scale (0, very disturbed; 3, completely refreshing); patient-reported physical well-being; patient satisfaction; pain evaluation; physical and mental health
De Salve[36] (2016)	Observational, open-label study in 52 elderly patients with moderate-to-severe chronic pain	Tapentadol PR for 90 days	Pain intensity at rest and at movement NRS baseline to end of treatment: –2.6 points	Quality of sleep (using a 4-point verbal scale from 0 to 3 (0, disturbed; 1, with frequent awakenings; 2, good; 3, very effective)); overall efficacy; mini mental state examination; QoL; activities of daily living and instrumental activities of daily living; number of responders

CIRS, cumulative illness rating scale; ER, extended release; NRS, Numerical Rating Scale; PD-Q, PainDETECT Questionnaire; PR, prolonged release; QoL, quality of life.

Table 2. Pain profile and analgesic treatment details of the pooled studies.

Study	Type of pain	Previous or concomitant treatment	Tapentadol dosage	Numerical Rating Scale
Panella et al.[29] (2016)	144 adult patients of both sexes who had undergone knee replacement surgery, with moderate-to-severe pain (baseline NRS ≥5) were admitted to the study 73.6%: continuous; 22% intermittent; 3.3% episodic; 1.1% intermittent/episodic	30% of the patients, all in the tapentadol group, had been treated previously with an analgesic, generally paracetamol alone or in association with NSAIDs	Over the course of the study, 43 of the patients in the tapentadol PR group did not change the initial dosage, 18 patients increased it, 9 reduced it, and in 21 patients the initial dose was modified, both increasing and decreasing it (20 receiving 50 mg bid and one receiving 100 twice daily)	Baseline: 5.2 End of treatment: 0.9
Notaro[30] (2017)	27 patients with chronic LBP 88.9% had suffered from LBP for >12 months 40.7% had neuropathic pain	All patients had already been treated with analgesic drugs	Tapentadol was more frequently prescribed at the initial dose of 100–200 mg/day; after 21 days of therapy, the most frequently dose applied was 300 mg/day	Baseline: 5.4 End of treatment: 1.7
Aurilio[32] (2019)	Patients with persistent moderate-to-severe chronic pain from different aetiologies (20% neck pain, 15% backbone osteoarthritis, 15% small joints osteoarthritis, 25% LBP and sciatic nerve pain, 10% hip or knee osteoarthritis) Pain was either nociceptive or neuropathic in 20% of cases and mixed in 80% of cases	70% of patients received NSAIDs, 15% paracetamol	The average dosage of tapentadol PR increased from 85 mg/day at T0 to 115 mg/day at T1, 136 mg/day at T2, 159 mg/day at T3, and 176 mg/day at T4*	Baseline: 6.8 End of treatment: 1.7
Orfei et al.[33] (2019)	25 patients with chronic pain 56% had nociceptive pain 44% had mixed pain 64% of patients reported continuous pain	Prior study intervention, 52% of patients had received paracetamol, 24% NSAIDs, 24% opioids	The average dosage of tapentadol PR at baseline was 130 mg/day and it increased at approximately 200 mg/day during follow-up, with a maximum dose of 300 mg/day	Baseline: 7.2 End of treatment: 2.4
Billeci et al.[34] (2017)	54 patients with moderate-to-severe chronic neck pain 74% had neuropathic pain	64.8% of patients received pharmacotherapy prior to study intervention	Tapentadol ER daily doses increased from 100 mg/day to a mean (standard deviation) dose of 204.5 (102.8) mg/day at the final evaluation	Baseline:6.8 End of treatment: 1.7

(Continued)

Table 2. (*Continued*)

Study	Type of pain	Previous or concomitant treatment	Tapentadol dosage	Numerical Rating Scale
Freo et al.[35] (2020)	65 young and 87 elderly patients with chronic LBP	Young (46% pregabalin/gabapentin; 28% NSAIDs, 18% antidepressant, 12% ASA) Elderly (44% ASA, 13% antidepressant, 3% pregabalin/gabapentin, 21% NSAIDs)	Young patients were started on tapentadol extended release 50 mg bid and older patients on 25 mg bid for 7 days; doses were then incremented by 50 mg every week In the case of intolerable side effects, tapentadol was down-titrated by 50 mg per week	Young Baseline: 7.4 End of treatment: 2.1 Elderly Baseline: 6.7 End of treatment: 2.3
Oriente[31] (2020)	35 patients had osteoporosis Pain was localized in the cervical spine in 82.9% of patients, lumbar spine in 82.6% and dorsal spine in 80.0%, and it was continuous in 77.1% of patients	94% of patients had already received analgesic therapy and >60% of patients were treated with paracetamol alone or in combination with opioids	At V0[§], the minimum and maximum dosages used were 50 mg and 100 mg twice daily, respectively, whilst at the visit V1 these values increased to 100 mg and 200 mg twice daily, respectively; on the following visits, the minimum dose increased to 200 mg/day, whilst the maximum dose stabilized at 400 mg/day and the median dose decreased to 150 mg/day and the minimum dose was 100 mg/day, whilst on day 180, the maximum dose was stable at 400 mg/day	Baseline: 5.4 End of treatment: 1.7
De Salve[36] (2016)	52 elderly patients with moderate-to-severe chronic pain 65.4% had mixed pain 26.9% had nociceptive somatic pain	94.2% of patients had already received analgesic therapy (15.4% paracetamol; 15.4% ibuprofen; 7.7% diclofenac; 7.7% diclofenac + codeine)	Only 21% of patients maintained the initial daily dose (50 mg); at the end of study, the mean daily dose was 150 mg and the maximum dose was 400 mg/die	Baseline: 5.2 End of treatment: 2.6

* The assessments were performed at baseline (T0), after 3–5 days with a phone call (T1), after 14–21 days (T2) and 30–40 days (T3) during regular outpatient visits in the ambulatory clinic, and at the end of the study (T4), after at least 90 days of treatment[32].
§ V0, baseline; V1, after 5 days of treatment[31]
ASA, aminosalicylate; LBP, low back pain; NSAIDs, nonsteroidal anti-inflammatory drugs; PR, prolonged release.

baseline to the end of the treatment period with mean differences in pain intensity ranging from –2.4 (ref.[29]) to –5.3.[35] Data on sleep quality were available for 442 patients (Table 3) and indicated that the percentages of patients reporting very disturbed sleep were lowered by tapentadol with a percent reduction ranging from 62.5% to 100%. Importantly, the documented significant pain relief from baseline (Table 1) was paralleled by an increased proportion of patients reporting good/restful sleep following treatment with tapentadol in all the analysed studies (Table 3), with a greater proportion of patients reporting good/restful sleep at the end of the study period compared to baseline (72.4% *versus* 25.3%; $p<0.01$) (Figure 1).

Overall, the reduction of patients rating their sleep quality as very disturbed sleep was reduced by 80% in the pooled patient population following tapentadol treatment regardless of the clinical setting, treatment duration, posology or patient age. Importantly, as the predominant sleep complaint reported by patients with CP is multiple nocturnal awakenings due to pain-related arousals throughout the night,[19] a 50% reduction in the frequency of night awakenings reported following tapentadol treatment may be of great clinical value from the patient perspective. In line with this, patient evaluation of overall health status and QoL was investigated by using the SF-12 questionnaire for both the mental and physical component in 275 patients with significant improvement (physical health: 45.8 *versus* 29.3, treatment difference 15.15, $p<0.01$; mental health: 57.10 *versus* 41.2, treatment difference 14.87, $p<0.01$) after tapentadol treatment. Furthermore, patients judged tapentadol treatment positively, with 70% of patients reporting a much/very much improved global health status as assessed by the patient's global impression of change (data available for 220 patients) (Figure 2). It should be emphasized that, in addition to the significant pain relief and the associated improved sleep quality, tolerability was also good (Figure 3) and no serious or severe adverse events occurred, with drowsiness reported in only one study[34] after 2 weeks of treatment but disappearing by the end of the treatment period. To date, tapentadol was found to be well tolerated in line with what has been previously reported in randomized clinical trials.[27,37,38]

Study limitations

This analysis itself is subject to limitations that are specific to real-world evidence studies, including low internal validity, lack of quality control surrounding data collection and susceptibility to multiple sources of bias for comparing outcomes. Furthermore, the retrospective nature of some of the findings may not exclude a risk of selection bias. Moreover, although this is a pooled analysis of real-world data, the overall number of patients included is not particularly high. This work was also limited by restricting its eligibility criteria to studies that include both measures of pain intensity and sleep quality as reported by the patients; overall, our work does not provide a robust basis for comparing treatment strategies. Of note, the analysis prevented the comparison with other opioids and did not allow a balanced consideration of the impact of treatment duration (which varies from 21 to 180 days in the analysed studies) and patient characteristics on the net benefit on sleep quality.

Discussion

The new definition of CP as a single disease entity, whose severity is best depicted through a multidimensional framework, acknowledges both the multidimensional nature of pain and the evolving notion of pain as a biopsychosocial issue and, more importantly, adds further emphasis to clinical outcomes that go beyond mere pain relief, namely QoL and functional recovery.[5,10,15] Improvement of such outcomes, which are highly valued by patients but judged by clinicians as rather subordinate to pain relief,[16] should be regarded as the main goal of an analgesic therapy. In this challenging scenario, the concept of functionality stands as an additional but relevant outcome that clinicians should keep in mind when selecting pain medications for patients with CP as it encompasses relevant domains of patients' QoL, including sleep quality. Poor sleep may predict the growth and intensification of pain over time,[18] with increased insomnia symptoms being both a predictor and an indicator of worse pain outcomes and physical functioning status over time.[1] Despite its importance, the impact of different analgesic therapies on QoL, functional recovery and sleep has been poorly assessed to date, whereas these evaluations may greatly help clinicians in the selection of treatment for patients with CP. By virtue of the two-sided relationship between pain intensity and sleep and the neurobiological link between pain control and the associated subjective improvement in sleep, we speculate that a reduction in pain intensity provided by tapentadol can improve sleep quality as well as favouring a better QoL. Therefore, pain reduction would be a necessary condition for sleep to improve.

Although we clearly recognize the limits of this statistical analysis, considering that patient population, painful conditions and even treatment duration were different in each study and therefore not directly comparable, our findings suggest that tapentadol provided significant pain control compared with baseline conditions, which was paralleled by subjective improvements in sleep quality in terms of a reduction in night awakenings and greater percentages of patients reporting restful sleep.[29–36] The findings of our pooled analysis showed a five-fold reduction in the frequency of very disturbed sleep following tapentadol treatment as well as a two-fold reduction in the predominant sleep complaint reported by CP patients – that is, nocturnal awakenings. Furthermore, a significantly greater proportion of patients reporting good/restful sleep at the end of the study period compared to baseline was also found (72.4% *versus* 25.3%; $p<0.01$). Of great value, this benefit was observed regardless of the clinical

Table 3. Proportion of patients reporting very disturbed sleep, frequent awakenings, good and restful sleep at baseline and at the end of study period for the eight studies included in the pooled analysis.

	Panella et al.[29] (2016)		Notaro[30] (2017)		Aurilio[32] (2019)		Orfei et al.[33] (2019)		Billeci et al.[34] (2017)		Freo et al.[35] (young cohort) (2020)		Freo et al.[35] (elderly cohort) (2020)		Oriente[31] (2020)		De Salve[36] (2016)	
	N	%	*N*	%	*N*	*N*	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
Baseline																		
Very disturbed sleep	15	16.5	3	15.0	2	10.0	3	13.6	33	34.7	20	36.4	26	44.1	18	50.0	2	4.5
Frequent awakenings	46	50.5	13	65.0	13	65.0	16	72.7	20	21.1	30	54.5	24	40.7	16	44.4	30	68.2
Good sleep	30	33.0	4	20.0	5	25.0	3	13.6	22	23.2	5	9.1	9	15.3	2	5.6	12	27.3
Restful sleep	0	0.0	0	0.0	0	0.0	0	0.0	20	21.1	0	0.0	0	0.0	0	0.0	0	0.0
Total	91	100.0	20	100.0	20	100.0	22	100.0	95	100.0	55	100.0	59	100.0	36	100.0	44	100.0
Final																		
Very disturbed sleep	4	4.4	0	0.0	0	0.0	0	0.0	6	6.3	5	9.1	7	11.9	0	0.0	0	0.0
Frequent awakenings	39	42.9	2	10.0	0	0.0	0	0.0	3	3.2	23	41.8	22	37.3	0	0.0	11	25.0
Good sleep	40	44.0	6	30.0	14	70.0	22	100.0	8	8.4	14	25.5	19	32.2	24	66.7	33	75.0
Restful sleep	8	8.8	12	60.0	6	30.0	0	0.0	78	82.1	13	23.6	11	18.6	12	33.3	0	0.0
Total	91	100.0	20	100.0	20	100.0	22	100.0	95	100.0	55	100.0	59	100.0	36	100.0	44	100.0

The sleep quality was mostly assessed on a 4-point scale (1, very disturbed; 2, with frequent awakenings; 3, good; 4, restful sleep) except for the study by Billeci et al., which evaluated pain-associated sleep interference assessed on a 11-point numerical rating scale (NRS) ranging from 0 (pain does not interfere with sleep) to 10 (pain completely interferes with sleep). In the latter case, the score was transformed in the Likert scale items according to the following rule: NRS ≥8, very disturbed sleep; NRS <8 to >5, frequent awakenings; NRS ≤5 to ≥3, good sleep; NRS <3, restful sleep. Overall, the sleep quality variable was analysed with the McNemar test extended to *n*×*n* contingency tables.

Figure 1. **Sleep quality at the end of the study period in patients with chronic pain receiving tapentadol prolonged release or extended release (pooled patient population). Comparisons between baseline values and last post-treatment values were performed using the nonparametric McNemar test for quality of sleep. Differences were considered as statistically significant for values of $p<0.05$. Statistical analysis was performed using SAS software V.9.4.**

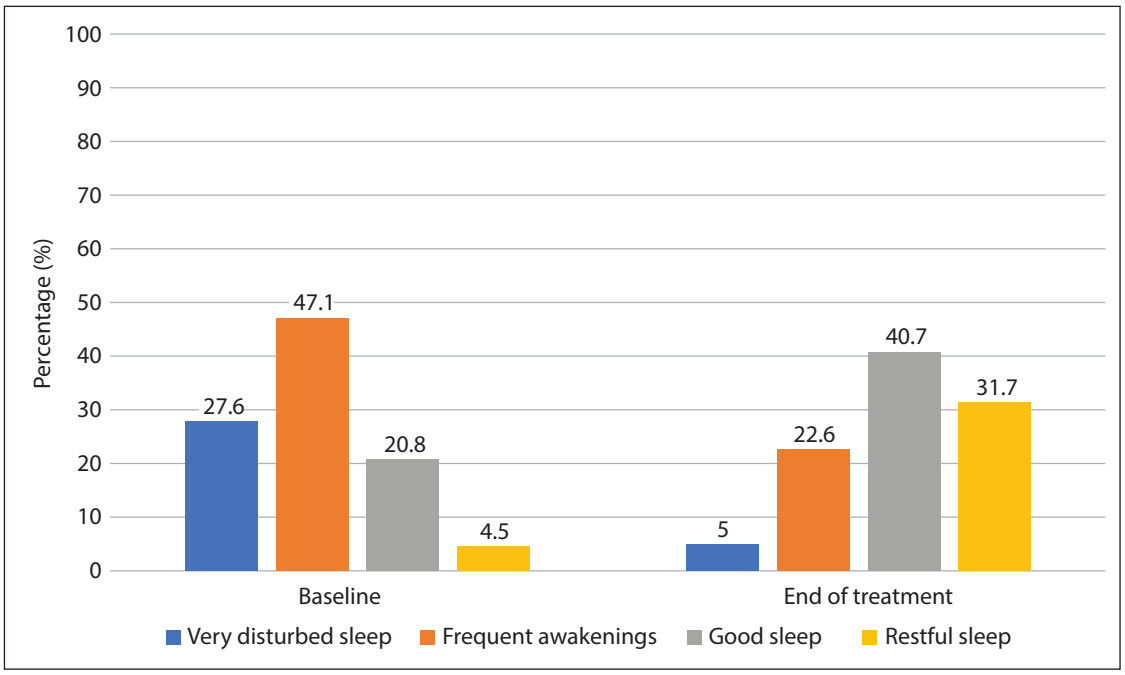


Figure 2. **Patient global impression of change at the end of the study period in patients with chronic pain receiving tapentadol prolonged release or extended release (pooled patient population). The Patient Global Impression of Change is only reported as descriptive statistics.**

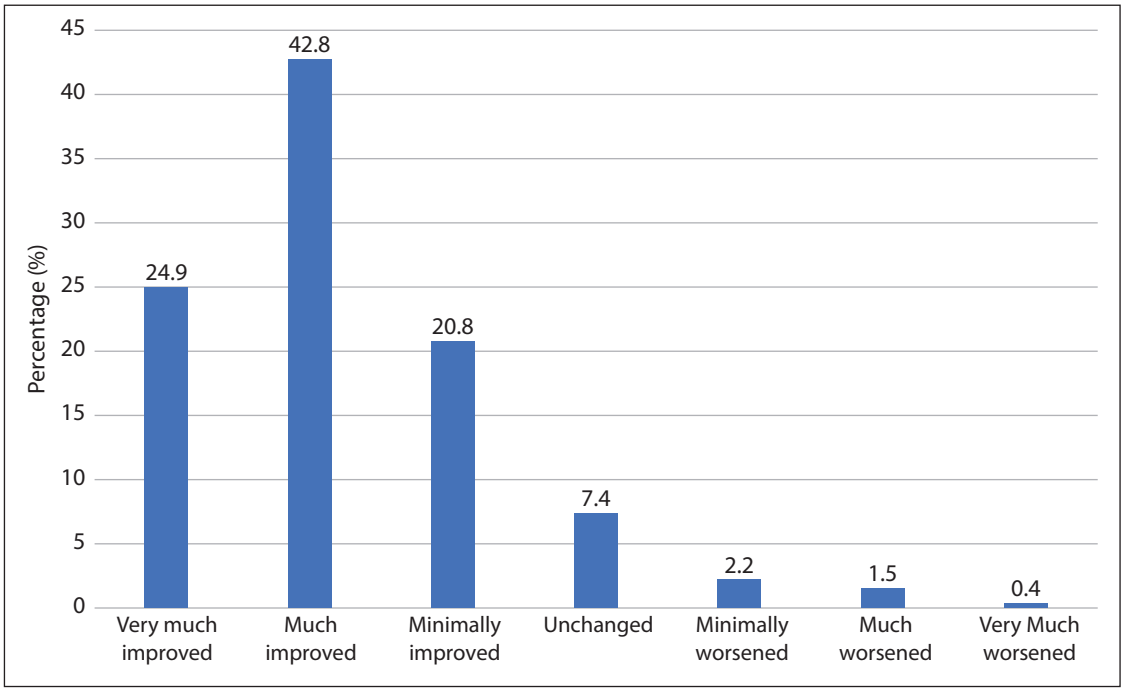
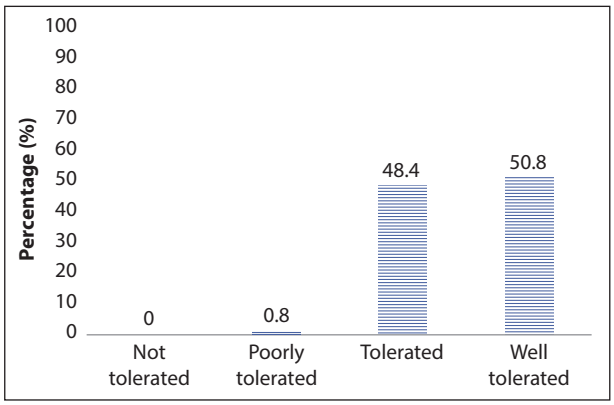


Figure 3. Tolerability at the end of the study period in patients with chronic pain receiving tapentadol prolonged release or extended release (pooled patient population). Tolerability is only reported as descriptive statistics.



setting, treatment duration, posology or patient age and was associated with a higher proportion of patients reporting an improved global health status and good tolerability, which is of utmost importance for a chronic condition.

Opioid therapy is known to affect sleep in different ways. Individuals on opioids report an increase in daytime somnolence, which may be related to higher doses of opioids but also give a subjective description of improved sleep quality. Thus, it is crucial to effectively discriminate the observed benefit on sleep quality from the somnolence that opioids may induce in CP patients. In this regard, a recent review examining the effects of opioid therapy on sleep in CP showed that, when an improvement in sleep could be observed, this was accompanied by daytime sleepiness and other undesirable side effects with 'somnolence', 'sedation', 'drowsiness' and 'sleepiness' being the most frequently reported sleep-related adverse event (AE).[39] In contrast, our analysis suggested that, in addition to the significant pain relief and the associated improved sleep quality, tolerability was also good, as no serious or severe adverse events occurred and drowsiness was reported as occurring in only one study[34] after 2 weeks of treatment but disappearing by the end of the treatment period. Of note, when assessing the outcome 'somnolence', there was evidence in favour of tapentadol when compared with oxycodone and oxymorphone.[40]

Conclusion

Our findings provide the rationale for addressing sleep quality as a relevant outcome, complementary to pain relief in CP management, and prompt us to further investigate the intimate link connecting pain control and sleep quality by designing studies involving polysomnography and measurements of total sleep time and sleep efficiency.

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