European Review for Medical and Pharmacological Sciences 2019; 23 (4 Suppl): 40-44

Tapentadol prolonged release in fragile geriatric patients > 70 years with chronic severe musculoskeletal pain: an open-label, prospective, observational study

C. AURILIO

Ambulatorio di Terapia Antalgica, Primo Policlinico Napoli, Naples, Italy

Abstract. – OBJECTIVE: Chronic pain is highly prevalent in the elderly, and the prolonged use of long-term opioids for the management of chronic musculoskeletal pain is controversial. Tapentadol, combining μ-opioid receptor (MOR) agonism and noradrenaline reuptake inhibition (NRI) in a unique mechanism of action, may be a valid option for chronic pain management in the geriatric population. The aim of the study was to assess the efficacy and tolerability of tapentadol prolonged release (PR), administered to patients aged ≥ 70 years with chronic pain.

PATIENTS AND METHODS: A total of 20 elderlies, naïve to opioids and with persistent moderate-to-severe chronic pain from different etiologies received tapentadol PR with up-titrations as necessary. The response to treatment, defined as at least 30% reduction in pain intensity compared with baseline, was the primary endpoint. Secondary endpoints were pain intensity on the Numeric Rating Scale (NRS) both at rest and during loading and sleep quality.

RESULTS: Tapentadol PR was safe and effective in our population of elderlies with chronic pain from different etiologies: pain intensity compared with baseline, both at rest and during load, was statistically lower at each visit ($p<0.01$), whereas sleep quality improved significantly throughout the study ($p<0.05$). Only few minor side effects were reported, with an overall good safety profile and a very high tolerability and satisfaction for treatment.

CONCLUSIONS: Tapentadol PR, adequately titrated according to patients' response in naïve subjects, is safe and effective to control pain in the elderly.

Key Words:
Chronic musculoskeletal pain, Elderly, Opioid therapy, Tapentadol.

Introduction

Musculoskeletal diseases affect hundreds of people worldwide[1,2], often determining severe long-term pain, especially in the elderly: according to a recent research, it has been estimated that two-thirds of the elderly suffer from chronic pain over at least 4 weeks[3,4]. Overall, the quality of life is also compromised by pain, due to the reduced mobility and physical activity, increased frailty with frequent falls, and poor sleep quality[5].

In the elderly, musculoskeletal diseases are often characterised by neuropathic pain and thus pharmacological therapies should mainly address this component of pain.

Tapentadol prolonged release (PR) is a centrally acting analgesic with a dual mechanism of action, combining μ-opioid receptor agonism (MOR) and noradrenaline reuptake inhibition (NRI). The 'μ-load' of tapentadol is ≤40% compared with pure MOR agonists[6] with a consequent improved tolerability compared with classical opioids, and a similar and reliable strength of analgesia for nociceptive, neuropathic, and mixed types of chronic pain[2,7,8]. Noteworthy, all these aspects of tapentadol translate into an overall improved quality of life of patients treated with this molecule[9]. Moreover, at early stages of pain, several functional and structural modifications occur, which may be restored if pain ceases promptly, or may remain permanently altered if pain persists. Thus, tapentadol PR may be considered a suitable option in patients with chronic pain, which is frequently associated to a strong component of neuropathic pain.

Given its characteristics, tapentadol PR can be an interesting analgesic option for geriatric patients, easily manageable, with limited adverse effects, and good analgesia, able to improve the overall quality of life and autonomy of these patients. Moreover, although a dose adjustment in the elderly is not required, the low-dose formulation (25 mg) may be more suitable for frail

Corresponding Author: Caterina Aurilio, MD; e-mail: caterina.aurilio@unicampania.it

elderlies in order to define the minimum effective dose in each individual patient.

Thus, further evidence on the efficacy and safety of tapentadol PR in the treatment of musculoskeletal pain in the elderly is necessary.

The aim of this study was to confirm the analgesic efficacy and tolerability of tapentadol PR in a sample of elderly fragile patients with chronic pain of different etiologies.

Patients and Methods

This study is an investigator-driven, prospective, open-label, observational study, conducted according to the Declaration of Helsinki after approval of the study protocol by the local Ethic Committee. All patients signed a written informed consent form before their inclusion in the study.

All patients of either gender aged ≥70 years, with chronic musculoskeletal pain higher than 5 on the Numeric Rating Scale (NRS), and naïve to opioids, were eligible to this study.

Exclusion criteria were as follows: (1): local or systemic infections able to interfere with pain self-assessment; (2) renal, liver or respiratory insufficiency; (3) recent (<6 months) history of major cardiovascular, neurological, endocrinological, gastrointestinal or oncological disease; (4) MAO therapy in the 14 days prior to enrolment; and (5) alcohol or drug abuse.

All patients received tapentadol PR (Grunenthal, Aachen, Germany) at a starting dose of 25 mg twice a day, which could be gradually increased according to clinical needs up to a maximum dose of 500 mg/day. Existing concomitant medications were maintained throughout the study.

The primary endpoint was the proportion of responder patients, defined as subjects who experienced a ≥30% reduction in pain intensity during loading on the NRS after 90 days of tapentadol treatment compared with baseline. Other endpoints were as follows: 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 assessed through the Mini-Mental State Examination; patients autonomy in both basic and instrumental activities of daily life the presence of neuropathic pain, assessed with the DN4 questionnaire; adherence to therapy assessed by the number and causes of drop-out.

Moreover, tolerability was evaluated in all patients by recording all side effects appearing within the study period, with particular attention being paid to severity, duration, and connection to the ongoing treatment. Furthermore, all vital signs (blood pressure, pulse, respiratory acts) were recorded for safety evaluations.

All the above-mentioned 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 our ambulatory clinic, and at the end of the study (T4), after at least 90 days of treatment. The last visit (T4) has been recorded and included in the present analysis even in case of earlier drop out of the patients from the study.

All patients evaluated the tolerability of the study treatment with a 4-point questionnaire (0 = poor; 4 = excellent).

Statistical Analysis

Statistical analysis was performed with Statistical Analysis System (SAS) 9.4 statistical software (SAS Institute, Cary, NC, USA). Data were analyzed by descriptive statistics; statistical comparisons were performed by the Student's *t*-test, the ANOVA test or the χ^2-test, as appropriate. A *p*-value of <0.05 was considered statistically significant.

Results

The study population consisted of 20 patients (seven males, 35%; mean age 73.4 years, age range 70-79 years). Pain etiology is reported in Table I. Table II shows concomitant disease. Ten patients (50%) reported pain over the last 3 months; in

Table I. Pain etiology.

Chronic non-oncologic pain	n	%
Low back pain	1	5.0
Low back pain and sciatic nerve pain	5	25.0
Neck pain	4	20.0
Hip osteoarthrosis	2	10.0
Knee osteoarthrosis	2	10.0
Backbone osteoarthrosis	3	15.0
Small joints osteoarthrosis	3	15.0
Diabetic neuropathy	1	5.0
Other	0	0.0

Table II. Comorbidities.

Comorbidity	n	%
Pulmonary/respiratory	1	5.0
Endocrine	2	10.0
Neurologic	0	0.0
Liver disease	1	5.0
Renal disease	1	5.0
Cardiovascular disease	13	65.0
Other:	3	15.0
Hypercholesterolemia	1	5.0
Benign prostatic hypertrophy	1	5.0
Gastro-oesophageal reflux	1	5.0

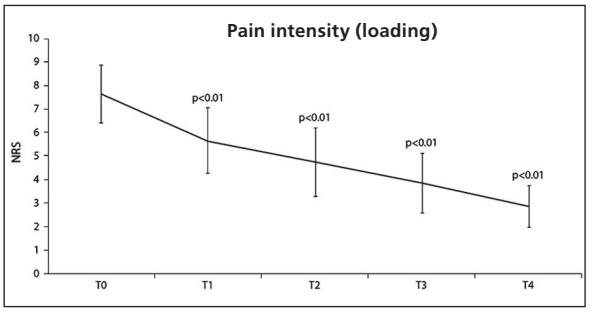

Figure 1. Pain intensity during loading assessed with the NRS.

three patients (15%) pain was present over the previous 3-6 months; the remaining seven patients (35%) experienced pain for longer than 6 months. Pain was either nociceptive or neuropathic in 20% of cases and mixed in 80% of cases. Continuous pain was reported by 12 patients (60%), intermittent pain by six patients (30%) whereas sporadic pain episodes were reported by two patients (10%). Previous analgesic therapy is shown in Table III. Noteworthy, the efficacy of previous analgesia was considered low or scarce by 18 patients, whereas its tolerability was graded as either very poor (four patients, 20%) or poor (16 patients, 80%). 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.

The primary endpoint of the study was reached, since at T4 all patients experienced the pre-specified ≥30% reduction in pain intensity during loading (Figure 1). In detail, the mean NRS score for pain intensity during loading decreased by 26%, from 7.6 to an average of 5.6, between T0 and T1. Later, pain intensity decreased by 38% at T2 (mean NRS = 4.7), by 50% at T3 (mean NRS = 3.8), and by 63% at T4 (mean NRS = 2.8; all $p<0.01$). Similarly, the mean NRS score for pain intensity at rest decreased by 24%, from 6.3 to an average of 4.8, between T0 and T1, by 41% at T2 (mean NRS = 3.7), by 49% at T3 (mean NRS = 3.2), and by 62% at T4 (mean NRS = 2.4; all $p<0.01$) (Table IV).

The quality of sleep improved throughout the study, as reported in Figure 2. The difference in the sleep quality between T0 and each following visit is statistically significant ($p<0.05$, McNemar test). The safety and tolerability of tapentadol were very good: only one patient (5%) reported a minor side effect, not requiring any specific treatment.

Only few patients completed the Mini-Mental State Examination, basic activities of daily life, instrumental activities of daily life, and DN4 questionnaires; therefore, these items were not considered for the final analysis due to a lack of consistent data.

Table III. Previous analgesic treatments.

	n	%
Coxib	1	5.0
NSAIDs	14	70.0
Miorelaxant	2	10.0
Paracetamol	3	15.0
Steroids	8	40.0

NSAIDs = non-steroidal anti-inflammatory drugs.

Discussion

Given the high frequency of side effects of opioids in the elderly, we tested whether tapentadol, an innovative and potent centrally acting MOR-NRI analgesic drug, could be a valuable alternative option for fragile geriatric patients suffering from chronic pain of different etiologies. Noteworthy, tapentadol shares half of the mechanism of action of strong opioids, through MOR, but its μ-load is less than 40% that of strong opioids[6], thus resulting in improved tolerability.

Aging is frequently linked to chronic painful conditions, due to frequent arthrosis, joints pain and several other painful diseases. It has been reported that up to 50% of elderly patients suffer from fastidious pain over at least 1 month. In our study, half of the study population experienced pain for at least 6 months.

Moreover, geriatric patients are at increased risk of drug interactions and adverse effects,

Table IV. Pain intensity at rest and during loading over the study period, with mean ± standard deviation.

NRS score	T0	T1	T2	T3	T4
Rest	6.3 ± 1.1	4.8* ± 1.5	3.7* ± 1.5	3.2* ± 1.3	2.4* ± 0.8
Loading	7.6 ± 1.2	5.6 ± 1.4	4.7 ± 1.5	3.8 ± 1.3	2.8 ± 0.9

*p<0.0001 *vs*. T0.

due to the increasing number of comorbidities, frequently associated with aging. Few recommendations[10-12] are available to guide therapy selection in this subpopulation of fragile geriatric patients. Despite the well-known side effects of NSAIDs in the elderly, these drugs are still over-used[13], although contraindicated. Conversely, a personalized approach to pain control often implies the use of opioids, which remain the first-choice analgesic option for chronic moderate-to-severe pain in the elderly. However, high doses of opioids may not always be enough to control neuropathic pain, despite several important side effects.

In our study, we found that tapentadol PR was well tolerated in a specific population of elderly subjects (≥ 70 years), in whom the side effects of opioids are usually more important. The benefits of tapentadol PR in our population consisted in improved pain control and sleep quality, translating into an overall improved general well-being. Unfortunately, we could not assess cognitive function and daily/instrumental life activity due to the lack of data recorded. However, several similar experiences in comparable populations of elderly patients show interesting results in favour of tapentadol PR[14].

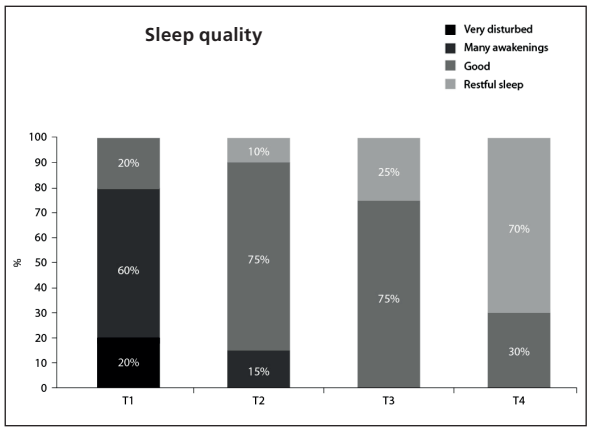

Figure 2. Sleep quality during treatment.

Conclusions

Our study focused on the management of chronic pain in a specific population of elderly patients, who frequently suffer from several comorbidities and are at increased risk of drug interactions and adverse effects. Opioids are commonly considered the first-choice analgesic option for chronic moderate-to-severe pain in the elderly. However, they carry on several serious adverse effects especially in fragile geriatric patients, and their efficacy against neuropathic pain may not always be good enough, with frequent therapy discontinuation.

The results of our study show that tapentadol PR, adequately titrated according to patients' response in naïve subjects, is safe and effective to control pain in the elderly. Moreover, therapy adherence remained high throughout the study period, only a few minor side-effects were reported, and the overall satisfaction for the analgesic treatment was very high.

Thus, tapentadol PR is not only very effective in controlling pain, but it also improves the overall quality of life through the improvement of sleep quality. This is of paramount importance especially in the elderly and more fragile patients who often experience generalized quality of life decrease linked to other treatments.

Key Points

- Tapentadol combines a reduced μ-opioid receptor agonism (<40%) with norepinephrine reuptake inhibition, thus being effective both on the nociceptive and neuropathic components of pain.
- Tapentadol PR was safe and effective in our population of elderlies with chronic pain from different etiologies.
- The reduction in pain intensity compared to baseline, both at rest and during load, was statistically significant at each visit (p<0.01).
- The quality of sleep improved significantly throughout the study (p<0.05).

- Only a few minor side effects were reported, with an overall good safety profile. Tolerability of tapentadol was very high, as expressed by patients' satisfaction for treatment.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

Medical writing for this paper was provided by Luca Giacomelli, Ph.D. This assistance and fees for publications were supported by Grunenthal. Editorial assistance was provided by Aashni Shah (Polistudium Srl, Milan, Italy), and was supported by internal funds.

References

1) Woolf AD, Erwin J, March L. The need to address the burden of musculoskeletal conditions. Best Pract Res Clin Rheumatol 2012; 26: 183-224.
2) Monti S, Caporali R. Chronic pain: the burden of disease and treatment innovations. Reumatismo 2015; 67: 35-44.
3) Shega JW, Tiedt A, Grant K, Dale W. Pain measurement in the national social life, health, and aging project (NSHAP): presence, intensity, and location. J Gerontol B Psychol Sci Soc Sci 2014; 69 Suppl 2: S191-197.
4) Malec M, Shega JW. Pain management in the elderly. Med Clin North Am 2015; 99: 337-350.
5) Blyth FM, Noguchi N. Chronic musculoskeletal pain and its impact on older people. Best Pract Res Clin Rheumatol 2017; 31: 160-168.
6) 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.
7) Coluzzi F, Fornasari D, Pergolizzi J, Romualdi P. From acute to chronic pain: tapentadol in the progressive stages of this disease entity. Eur Rev Med Pharmacol Sci 2017; 21: 1672-1683.
8) Sánchez Del Águila MJ, Schenk M, Kern KU, Drost T, Steigerwald I. Practical considerations for the use of tapentadol prolonged release for the management of severe chronic pain. Clin Ther 2015; 37: 94-113.
9) Buynak R, Rappaport SA, Rod K, Arsenault P, Heisig F, Rauschkolb C, Etropolski M. Long-term safety and efficacy of tapentadol extended release following up to 2 years of treatment in patients with moderate to severe, chronic pain: results of an open-label extension trial. Clin Ther 2015; 37: 2420-2438.
10) Hauser W, Schug S, Furlan AD. The opioid epidemic and national guidelines for opioid therapy for chronic non-cancer pain: a perspective from different continents. Pain Rep 2017; 2: e599.
11) Canadian guideline for safe and effective use of opioids for chronic non-nancer pain. Practice tool kits. Available at: www.nationalpaincentre. mcmaster.ca/documents/practicetoolkit.pdf. Accessed December 1, 2016.
12) CDC guideline for prescribing opioids for chronic pain—United States, 2016. Available at: https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1. htm. Accessed December 1, 2016.
13) Bally M, Dendukuri N, Rich B, Nadeau L, Helin-Salmivaara A, Garbe E, Brophy JM. Risk of acute myocardial infarction with NSAIDs in real world use: Bayesian meta-analysis of individual patient data. BMJ 2017; 357: j1909.
14) Biondi DM, Xiang J, Etropolski M, Moskovitz B. Tolerability and efficacy of tapentadol extended release in elderly patients ≥ 75 years of age with chronic osteoarthritis knee or low back pain. J Opioid Manag 2015; 11: 393-403.