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# Tapentadol prolonged release and the long-term management of chronic musculoskeletal pain in the elderly – focus on anxiety, depression, cognitive status and life quality: the TaPE study

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**Abstract. – OBJECTIVE: The use of long-term opioids for the management of chronic musculoskeletal pain is a hot topic in the scientific community, especially when it concerns the elderly. This paper aimed at assessing the efficacy and tolerability of tapentadol prolonged release (PR), a molecule with a unique mechanism of action combining μ-opioid receptor (MOR) agonism and noradrenaline reuptake inhibition (NRI), administered to patients aged ≥80 years with chronic persistent pain. The effect of this molecule on anxiety, depression, cognitive status, and overall quality of life were investigated.**

**PATIENTS AND METHODS: This was a spontaneous, observational, open-label, prospective study, in 80 older patients aged ≥80 years, naïve to strong opioids, presenting moderate-to-severe chronic pain from different etiologies. Tapentadol PR was initially prescribed at the dose of 25-50 mg/day and increased gradually in case of insufficient analgesia. Pain intensity was assessed by a 10-point Numeric Rating Scale (NRS). Other endpoints were as follows: DN4 questionnaire for the evaluation of the neuropathic component of pain, SF12, HADS, and MMSE questionnaires to evaluate the quality of life, anxiety, and cognitive impairment, respectively. Safety evaluations were also performed through the assessment of the frequency and severity of adverse events.**

**RESULTS: At T45, NRS score reduction was achieved in 86.0% of patients. On average, pain decreased by 55% from a mean of 8.2 to a mean of 3.6. At T90, tapentadol PR did not affect the psychophysical and cognitive abilities of older patients.**

**CONCLUSIONS: The benefits with tapentadol PR in controlling pain have improved the quality of life of our patients, also showing a favorable effect on their cognitive performance.**

*Key Words:*
Chronic musculoskeletal pain, Elderly, Opioids therapy, Tapentadol.

## Introduction

Musculoskeletal diseases represent a clinically and socio-economically relevant issue involving hundreds of people worldwide[1,2]. The burden of these conditions can be further increased when severe long-term pain occurs. Remarkably, long-term pain is common in the elderly: it has been reported that at least two out of three people aged >75 years suffer from chronic pain [Numeric Rating Scale (NRS) ≥5] over a period of at least 4 weeks[3,4]. Pain negatively impacts on several other aspects of healthcare, such as low physical activity, poor mobility, frailty, depression, cognitive impairment, falls, and poor sleep quality[5].

Older people with musculoskeletal diseases often experience neuropathic pain and central pain syndromes. Therefore, pharmacological therapies must be able to address also these components of pain.

Tapentadol prolonged release (PR) is a centrally acting analgesic with a double synergistic mechanism of action [μ-opioid receptor (MOR) agonism and noradrenaline reuptake inhibition (NRI)]. It provides strong and reliable analgesia across a range of indications, including nociceptive, neuropathic, and mixed types of chronic pain. Moreover, it is associated with an improved tolerability profile relative to classic opioid anal-

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gesics[2,6,7]. Noteworthy, these benefits are paralleled by improvements in overall quality of life (QoL)[8]. Therefore, tapentadol PR may be considered a suitable option in patients with chronic pain, given the frequent neuropathic component of this condition. However, further evidence on the efficacy and safety of tapentadol PR in the treatment of musculoskeletal pain in the elderly is mandatory.

## Patients and Methods

### Study Setting and Design

This study was an investigator-driven, prospective, open-label, observational study, conducted by the Pain Therapy Centre of the Italian National Research Center on Aging (INRCA-IRCCS). The study was conducted according to the Declaration of Helsinki from November 2015 to July 2016, after approval of the study protocol by the local Ethics Committee. All patients signed a written informed consent before inclusion in the study.

### Patients

Patients of either gender aged ≥80 years affected from musculoskeletal pain higher than 5 on the NRS, for more than 3 months were eligible to this study.

Exclusion criteria were as follows: (i): local or systemic infections able to interfere with pain self-assessment; (ii) renal, liver, and respiratory insufficiency; (iii) recent (<1 year) history of major cardiovascular, neurological, endocrinological, gastrointestinal or oncological disease; (iv) monoamine oxidase therapy in the 14 days prior to enrollment; and (v) alcohol abuse.

### Treatment and Follow-Up

All patients received tapentadol PR (Palexia®, Grunenthal, Aachen, Germany) at a starting dose of 25/50 mg/day, which could be gradually increased according to clinical needs up to a maximum dose of 500 mg/day. In case of poorly controlled pain, adjuvant treatments for the neuropathic and inflammatory component of pain could be added as per clinical need.

### Endpoints

The primary endpoint was the proportion of responder patients, defined as subjects who experienced a reduction of ≥30% in pain intensity on the NRS compared with baseline after 45 days of tapentadol treatment. Other endpoints were as follows: DN4 questionnaire for evaluation the neuropathic component of pain, SF12, HADS, and MMSE questionnaires to evaluate QoL, anxiety and cognitive impairment, respectively. The safety evaluations were performed by assessing frequency and severity of adverse events (AEs) according to the CTCAE, version 4.0.

All the above-mentioned assessments were performed at baseline (V0), and after 7 (V7), 15 (V15), 45 (V45), and 90 (V90) days of tapentadol therapy. At V45, patients provided an additional evaluation of the improvement of their painful condition, compared to baseline, on a 7-point scale (1=very much improved). At the end of the follow-up period (V90), the efficacy and safety of tapentadol therapy was evaluated according to a 4-point scale (0=not effective or very poorly tolerated).

### Statistical Analysis

All data were analyzed by descriptive statistics and with non-parametric tests. The R 3.0.5 software (R Foundation for Statistical Computing, Vienna, Austria) was used for all analyses.

## Results

We enrolled 80 patients, mean age 83 ± 0.2 years (age range: 80-93 years), with 57 patients (71%) being females. Osteoarthrosis was the most frequent condition causing pain (n=40; 51%), followed by low back pain (n=17; 22%). In total, 57% of patients suffered from chronic pain for up to 6 months (23% for less than 3 months, 34% for 3-6 months), with the remaining 43% of patients experiencing pain over at least 12 months. NSAIDs were the most commonly prescribed analgesic drugs (n=46, 58%) with 11 patients (14%) not receiving any analgesic therapy before tapentadol (Table I). Overall, 52 patients completed the study to V90.

According to sample size calculations, the satisfactory percentage of patients to assess the primary endpoint at V45 was 70%. Thus, the 57

**Table I.** Concomitant analgesic treatments.

| | n | % |
|---|---|---|
| NSAIDs | 46 | 58 |
| Opioids and adjuvants | 13 | 16 |
| Other | 9 | 11 |
| Antalgic block joints | 1 | 1 |
| No therapy | 11 | 14 |

NSAIDs = non steroidal anti-inflammatory drugs.

**Table II.** Number of patients reporting each NRS over the study, with mean and standard deviation (SD).

| NRS score | V0 | V7 | V15 | V45 | V90 |
|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 1 | 0 |
| 1 | 0 | 0 | 0 | 0 | 0 |
| 2 | 0 | 0 | 2 | 12 | 16 |
| 3 | 0 | 3 | 10 | 21 | 18 |
| 4 | 0 | 8 | 22 | 10 | 10 |
| 5 | 1 | 15 | 14 | 4 | 3 |
| 6 | 2 | 23 | 8 | 3 | 2 |
| 7 | 15 | 17 | 5 | 4 | 2 |
| 8 | 35 | 4 | 4 | 1 | 0 |
| 9 | 18 | 3 | 0 | 0 | 0 |
| 10 | 8 | 0 | 0 | 0 | 0 |
| Mean | 8.2 | 5.9 | 4.7 | 3.6 | 3.3 |
| SD | 1.0 | 1.4 | 1.4 | 1.6 | 1.3 |

patients who completed the V45 follow-up and corresponded to 71.25%, were sufficient for primary endpoint evaluation.

### NRS Analysis

Mean intensity of pain at baseline was 8.2 (range: 5-10). At V45, the proportion of responders was 71%, with 49 experiencing at least a 30% decrease in pain (85.96%), on average, from 8.2 to 3.6 ($p$=0.9985).

Table II presents the change in pain intensity over time: a constant decrease of this parameter was observed throughout the study, and its significance was verified through the Wilcoxon test, confirming that $p$<0.0001 for NRS values was significantly lower.

### DN4 Questionnaire

At V0, the DN4 score was 4.9 ± 1.7 (range: 1-8). This value decreased during therapy to 3.2 at V45 (range: 0-7). At the end of the study, the DN4 score was 2.0 ± 0.9, with a low variability index. The analysis by Wilcoxon test confirmed the statistically significant variation of DN4 scores both between V0 and V45 and between V45 and V90, with $p$<0.0001. Among the 57 patients who completed visit V45, the DN4 score was lower than DN4 score at V0 in 51 patients (89.5%). The decrease of DN4 scores between V45 and V90 was less pronounced, with 75% of patients experiencing a reduction of the score.

### QoL Assessments

QoL was measured with the three questionnaires SF12, HADS, and MMSE at each visit. For SF12 and MMSE the scores progressively increase with the increase of patients' well-being. On the contrary, in the HADS questionnaire the improvement of anxiety and depression is expressed by a decrease of the questionnaire score. Each variation was evaluated with the Friedman and Wilcoxon tests, in order to evaluate the significance of the variations registered. The results of the Friedman test showed that effectively the values recorded for the questionnaires follow the optimal trend: they increase for SF12 and MMSE and decrease for HADS. In all cases $p$<0.0001 makes this result statistically significant. The Wilcoxon test, on the other hand, showed that the most significant variations happened in the first 45 days of therapy; the transition from previous therapy to tapentadol therapy, even at low doses, carries on improvements from the beginning.

Regarding the HADS questionnaire, anxiety improved in 43 patients out of 57, with lower values of the questionnaire in the first 45 days of treatment; in 13 patients the variation was unclear, whereas in one patient the score of anxiety was increased. Depression improved in 44 patients during the first 45 days of treatment.

The SF12 physical and mental status questionnaires both improved in 44 patients from V0 to V45 and in 36 from V45 to V90.

The MMSE test showed more stable values, since the patients' cognitive status does not often correlate with pain and thus it may not show variations.

### Patients' Evaluation

At the end of the study (V90), patients were asked to evaluate their general conditions after starting the study treatment. Patients' opinions were expressed on a 1-7 scale, with "1" being "Improved a lot" and 7 "Worried a lot". Among the patients who completed the study and answered the final questionnaire, all patients expressed satisfaction for the treatment received, registering an improvement in their general condition.

## Discussion

Opioids are often considered responsible for cognitive side effects in patients, especially in the elderly. We tested tapentadol, a new and potent centrally acting as a MOR-NRI analgesic drug, in a population of very elderly patients with chronic pain of different etiologies. We found that tapentadol PR was effective in this specific population of elderly subjects (≥80 years), who improved not only their painful condition but also their general well-being.

Aging is frequently linked to an increase in chronic painful conditions (arthrosis, joints pain, etc). Several cohort studies reported that up to 50% of the interviewed sample suffered from bothersome pain in the previous month. A further increase in that figure was reported when elderly people over 85 years of age were considered: in this subgroup, up to 79% of patients reported pain over at least 1 month.

With these data in mind, we focused our research project on the management of chronic pain in this specific population of elderly, who frequently suffer from several comorbidities and who are at increased risk of drug interactions and adverse effects. The scientific community has been discussing about three specific alerts in the elderly: 1) the risks linked to the treatment with opioids in these patients[9,10]; 2) the search for new molecules acting directly on pain pathogenic pathways, such as for inflammatory and degenerative musculoskeletal diseases; and 3) the improvement of opioids tolerability profile through the search of new molecules with combined opioid and other action.

In Italy, the international recommendations and guidelines[9-11] are far from being correctly and systematically applied: NSAIDs are still over-used despite their well-known side effects in the elderly[12], in whom they should be contra-indicated.

We prefer a "personalized" approach to pain control, which often implies the use of opioids. These drugs are still the first-choice analgesic option for chronic moderate-to-severe pain in the elderly. However, opioids may not always be enough to control several chronic painful conditions, such as complex syndromes, and the increase in their dosage is responsible for a limited therapy adherence. In fact, higher doses of opioids are often useless to control several components of chronic pain, such as neuropathic pain, and they are prone to several side effects.

The results of our study are in line with previous findings[7], where low doses of tapentadol, adequately titrated according to patients' response in naïve subjects, are safe and effective to control pain in the elderly. A limited number of minor adverse effects was noted only at the beginning of treatment, and with goal-directed and adequate patients' information therapy adherence remained high throughout the study period.

## Conclusions

Overall, the benefits obtained with tapentadol in controlling pain have improved the quality of life of our patients, also showing a favorable effect on their cognitive performance. This fact should be regarded as an important element to consider for the overall well-being of patients, especially among the elderly and more fragile patients who often suffer from generalized QoL decrease with other treatments.

### Conflict of interest

All Authors declare to have no competing interests with this manuscript.

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