# Cost-Effectiveness Analysis of Tapentadol PR Versus Oxycodone/Naloxone PR in Patients with Musculoskeletal Pain in Spain

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**Abstract**

**Objetive:** Chronic musculoskeletal pain is highly prevalent worldwide and is associated with a huge social and economic burden. Opioids are commonly prescribed to treat chronic pain as recommended by the European Pain Federation. Tapentadol prolonged release (PR), is a strong opioid that has proven being effective in treating chronic musculoskeletal pain with less adverse events than oxycodone/naloxone PR. The aim of this study was to estimate the cost-effectiveness of tapentadol PR compared to oxycodone/naloxone PR from the Spanish National Healthcare System perspective (SNHS).

**Methods:** A Markov model was adapted analysing two arms: patients treated with tapentadol PR and patients treated with oxycodone/naloxone PR. The model assesses a cohort of 1,000 patients over a one-year period.

**Results:** Overall, treating patients with tapentadol PR was less costly than treating patients with oxycodone/naloxone PR (€388,631.70 vs €568,168.85). In terms of cost effectiveness, the incremental cost of tapentadol PR over oxycodone/naloxone PR was -€179,537.15 and the incremental quality-adjusted life year value was 40.05. The incremental cost-effectiveness ratio was estimated at -€4,027.16 per quality-adjusted life year suggesting that tapentadol PR is an economically dominant alternative over oxycodone/naloxone PR.

**Conclusion:** Tapentadol PR represents a cost-effective option to treat musculoskeletal chronic pain patients in Spain.

**Keywords:** Musculoskeletal pain, Opioids, Tapentadol PR, Cost effectiveness, Spain.

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## INTRODUCTION

Approximately 1.71 (95 % Confidence interval (CI):1.68-1.80) billion people globally live with musculoskeletal disorders[1], with pain being a common symptom which can acutely or chronically involve bones, muscles, ligaments, tendons and nerves[2]. Among this type of disorders 568 (95% CI: 505-640) and 223 (95% CI: 179-281) million people worldwide have low back pain and neck pain, respectively[1]. Low back pain causes the highest burden with 64 million (95% CI: 45-85) life years of disability worldwide[1].

The International Association for the Study of Pain (IASP) defines chronic pain as pain persisting beyond a period of 3 months[3]. In Europe, 35.7% (95% CI: 34.9%-36.5%) of the population over 50 years of age reported suffering from chronic musculoskeletal pain[4]. Such pain can drastically impair daily activities, working abilities and reduce quality of life. In high income countries, it is known to be the leading cause of disability bearing a huge economic and social cost[2,5].

In Spain, the prevalence of musculoskeletal pain among people aged 50 years old and more was estimated to be 36.6% (95% CI: 34.2%-39.0%)[4]. In 2007, it led to a loss of 23% of working days, which in economic terms amounted to 1,702 million euros[6]. According to the European Pain Federation, opioid treatment can be considered in selected, highly monitored patients, if established non-pharmaceutical treatments or non-opioid analgesics are ineffective, contraindicated, or not tolerated[7]. An individualized, patient-centred approach for the diagnosis and treatment of pain and considering patient variables that may affect opioid dose for each patient prior to opioid use, is essential[8].

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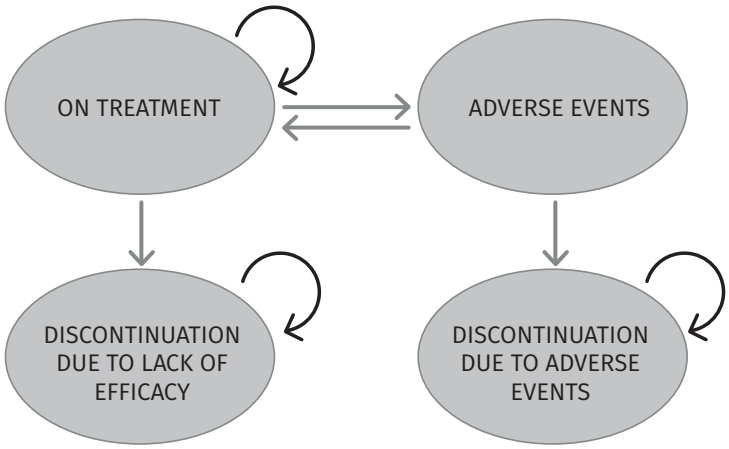
Tapentadol is a strong opioid which centrally acts as an analgesic through two mechanisms of actions: μ-opioid receptor agonism and noradrenaline reuptake inhibition[9,10]. In Spain, tapentadol was authorized in 2010 and is indicated for the relief of severe chronic pain in adults, who can only be managed with an opioid analgesic[11]. In clinical trials, tapentadol has demonstrated superiority over oxycodone/naloxone prolonged release (PR) in reducing pain intensity among patients suffering from severe chronic low back pain (LBP) with a neuropathic component[12]. Moreover tapentadol was associated with a significant greater quality of life and a reduced risk of treatment discontinuation than oxycodone/naloxone PR[13]. Therefore, the aim of this study was to estimate the cost-effectiveness of tapentadol PR compared to oxycodone/naloxone PR in patients with chronic musculoskeletal pain in Spain that require treatment with a strong opioid.

**FIGURE 1**

MARKOV MODEL




Markov model illustrating the different health states a patient can transit to.

Reference: Own elaboration.

## METHODS

### Model Structure

A Markov model previously developed for Italy, in Microsoft Excel, was adapted to the Spanish National Healthcare System. The model consists of a hypothetical cohort of 1,000 patients over a one-year time horizon and compare two arms: patients with musculoskeletal pain treated with tapentadol PR and patients with musculoskeletal pain treated with oxycodone/naloxone PR. The model included four health states (Figure 1): on treatment, adverse events, discontinuation for adverse events and discontinuation due to lack of efficacy. Death was not included as a health state in this model as the time horizon considered was too short. All patients enter in the model in the "on treatment" state. From the "on treatment" state, patients may experience adverse events, a discontinuation due to adverse events or due to lack of efficacy. The duration of the cycles was 90 days. Transition probabilities through the different health states for the tapentadol PR and oxycodone/naloxone PR treatments, were derived from a tapentadol PR randomized clinical trial (Table 1)[12].

### Utilities and Costs

Utilities and costs were allocated for each health state. Utilities were obtained from the literature (Table 2)[14]. The costs included

**TABLE 1**

TRANSITION PROBABILITIES

| | Adverse reaction | Discontinuation (adverse reaction) | Discontinuation (non-effective) |
|---|---|---|---|
| Tapentadol PR | 0.2308 | 0.2000 | 0.0615 |
| Oxycodone/naloxone PR | 0.4219 | 0.4063 | 0.1328 |

Abbreviations: PR: prolonged release.

Reference: Baron et al., 2016[12]


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**TABLE 2**

UTILITIES

| | Treatment | Adverse reaction | Discontinuation (adverse reaction) | Discontinuation (non-effective) |
|---|---|---|---|---|
| Tapentadol PR | 0.695 | 0.583 | 0.503 | 0.405 |
| Oxycodone/naloxone PR | 0.695 | 0.583 | 0.503 | 0.405 |

**Abbreviations**: PR: prolonged release.

**Reference: Obradovic et al., 2012**[14]

were pain medications, adverse events, and discontinuation due to lack of efficacy and adverse events. All costs were expressed as 2022 euros[15].

Drug costs were extracted from the General Pharmaceutical Council's database[16]. Only financed and commercialized drugs in Spain were considered for the model. Pain treatment costs are shown in Table 3.

For adverse events and discontinuation due to lack of efficacy and adverse events costs, specialist visits, treatment with metoclopramide and generic laxatives for nausea, vomiting or constipation, and hospitalizations were considered[14]. Table 4 shows the unit costs and the resource use required per month[15,16,18–36]. The visit and hospitalization costs were extracted from the median value of each Spanish Autonomous Communities unit costs[15,19–36] and from the Spanish Ministry of Health database, respectively[15,18]. Finally, the unit costs of adverse events, discontinuation due to adverse events, and discontinuation due to lack of efficacy were estimated at €245.79, €142.30 and €269.12 respectively[15,16,18–36].

### Cost-effectiveness

A willingness to pay (WTP) threshold of €25,000 per quality-adjusted life year (QALY) was considered for this model as recommended in Spain[37,38]. Cost effectiveness was expressed in this model in terms of Incremental Cost-Effectiveness Ratio (ICER)[39].

### Sensitivity Analysis

A univariate deterministic sensitivity analysis (DSA) and a probabilistic sensitivity analysis (PSA) were carried out to demonstrate the robustness of the results. The univariate DSA varied the following parameters by +/- 20%: utility of discontinuation due to inefficacy, utility of adverse events, utility of discontinuation due to adverse events, mean cost of adverse events, mean cost of discontinuation due to inefficacy, mean cost of discontinuation due to adverse events and utility of being on treatment. The PSA was performed including 1,000 simulations of the cohort. The parameters were independently varied according to different distributions (gamma distribution for costs, and a beta distribution for utilities and transition probabilities) and point estimates were drawn using a Monte Carlo simulation.

**TABLE 3**

PAIN TREATMENT COSTS

| | Cost/mg | Cost/day | Cost/cycle |
|---|---|---|---|
| Tapentadol PR | € 0.0047 | € 0.4700 | € 42.30 |
| Oxycodone/naloxone PR | € 0.0194 | € 0.5807 | € 52.26 |

**Abbreviations**: PR: prolonged release.

**Reference: Consejo General de Colegios Oficiales de Farmaceuticos (CGCOF)**[16]

**TABLE 4**

RESOURCES USE AND COSTS PER HEALTH STATE

| Discontinuation for lack of efficacy | Unit cost | Frequency/month | Cost/month | Cost/cycle* |
|---|---|---|---|---|
| Visit to a specialist | € 91.31 | 0.950 | € 86.74 | € 260.23 |
| Generic laxatives (7g/day)** | € 0.13 | 2.450 | € 0.32 | € 0.96 |
| Magnesium hydroxide 2.4g/day (1 sachet) ** | € 0.11 | 2.450 | € 0.28 | € 0.84 |
| Metoclopramide 30ml/day | € 0.19 | 9.240 | € 1.77 | € 5.32 |
| Hospitalization for severe adverse event in rheumatology | € 117.19 | 0.005 | € 0.59 | € 1.76 |
| **Total cost** | | | **€ 88.06** | **€ 269.12** |
| **Discontinuation for adverse events** | **Unit cost** | **Frequency/month** | **Cost/month** | **Cost/cycle*** |
| Visit to a specialist | € 91.31 | 0.490 | € 44.74 | € 134.23 |
| Generic laxatives (7g/day)** | € 0.13 | 1.350 | € 0.18 | € 0.53 |
| Magnesium hydroxide 2.4g/day (1 sachet) ** | € 0.11 | 1.350 | € 0.15 | € 0.46 |
| Metoclopramide 30ml/day | € 0.19 | 9.240 | € 1.77 | € 5.32 |
| Hospitalization for severe adverse event in rheumatology | € 117.19 | 0.005 | € 0.59 | € 1.76 |
| **Total cost** | | | **€ 46.58** | **€ 142.30** |
| **Adverse events** | **Unit cost** | **Frequency/month** | **Cost/month** | **Cost/cycle*** |
| Visit to a specialist | € 91.31 | 0.870 | € 77.44 | € 238.32 |
| Generic laxatives (7g/day)** | € 0.13 | 0.525 | € 0.07 | € 0.21 |
| Magnesium hydroxide 2.4g/day (1 sachet) | € 0.11 | 0.525 | € 0.06 | € 0.18 |
| Metoclopramide 30ml/day | € 0.19 | 9.240 | € 1.77 | € 5.32 |
| Hospitalization for severe adverse event in rheumatology | € 117.19 | 0.005 | € 0.59 | € 1.76 |
| **Total cost** | | | **€ 88.06** | **€ 269.12** |

*Cycle lasts 90 days; **The generic laxatives financed in Spain have been included: Plantago ovata and magnesium hydroxide with a 50% distribution for both drugs.

References: Consejo General de Colegios Oficiales de Farmacéuticos (CGCOF)[16]; Ministerio de sanidad, 2020[15,18]; Median value of the unit costs for Spanish Autonomous communities[15,19–36]; Obradovic M et al., 2012[14].

## RESULTS

### Base Case and Scenario Analysis

Overall treating a cohort of 1,000 patients with tapentadol PR was less costly than treating patients with oxycodone/naloxone PR (€388,631.70 vs €568,168.85). Pharmacological cost was reduced by 4.1% in the tapentadol arm (€150,635.90 vs. €157,032.08), while the costs associated with treatment discontinuation and adverse events were reduced by 42.1% (€237,995.80 vs. €411,136.77). In addition, an incremental 40.05 QALYs would be generated, as 650.78 and 610.73 QALYs would be obtained in the tapentadol PR and oxycodone/naloxone PR, respectively. Therefore, the results (Table 5) suggest that tapentadol PR is dominant, as it is less costly and brings additional health benefits compared to oxycodone/naloxone PR.

### Sensitivity Analysis

The tornado graph summarises the results of the univariate DSA (Figure 2). Overall, tapentadol PR remained a dominant alternative as the ICER remained negative in all cases. The most significant change was triggered by varying the

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**TABLE 5**

RESULTS

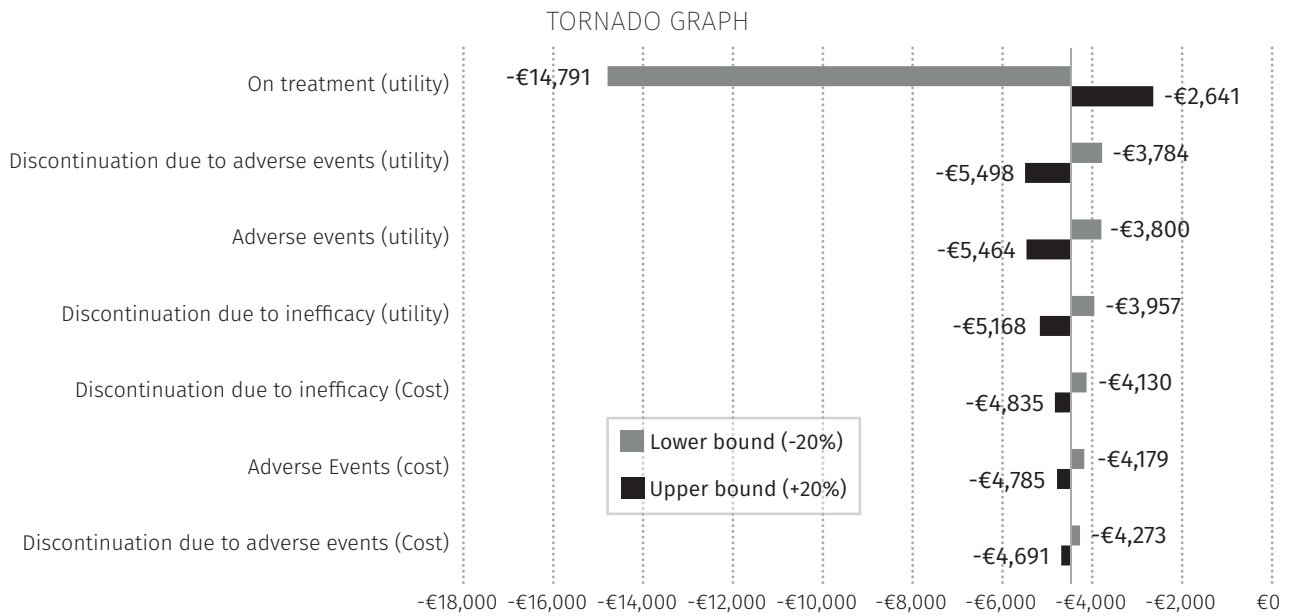
| | Tapentadol PR | Oxycodone/naloxone PR |
|---|---|---|
| **Total cost** | € 388,631.70 | € 568,168.85 |
| Treatment cost | € 150,635.90 | € 157,032.08 |
| Adverse event cost | € 135,737.97 | € 192,400.98 |
| Discontinuation cost | € 102,257.83 | € 214,735.79 |
| **Total QALYs** | 650.78 | 610.73 |
| **Incremental cost** | -€ 179,537.15 | |
| **Incremental QALY** | 40.05 | |
| **ICER** | Dominant (-€ 4,482.27/ QALY) | |

**Abbreviations: ICER**: incremental cost-effectiveness ratio; **QALY**: quality-adjusted life year; **PR**: prolonged release.

**Reference: own elaboration.**

on-treatment utility parameter compared to the base case scenario. The results of the PSA showed that all simulations were located in the upper left quadrant of the cost-effectiveness plane (Figure 3). The results of the PSA showed that 99.60% of the simulations were cost-effective and that 99.10% were dominant with a threshold of €25,000/QALY[37] (Figure 4). The ICER ranged from -€159,800.96/QALY to €130,465.96/QALY.

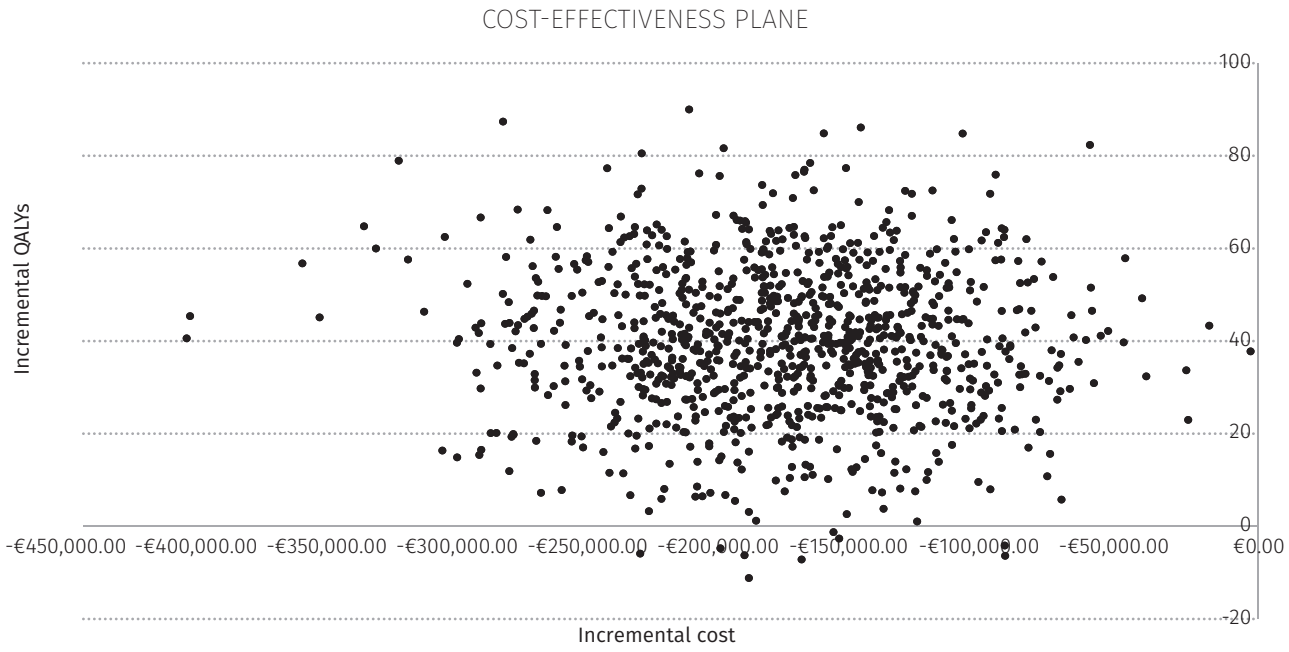
**FIGURE 2**




Tornado graph summarizing the results of the deterministic univariate sensitivity analysis.

**Reference: own elaboration.**

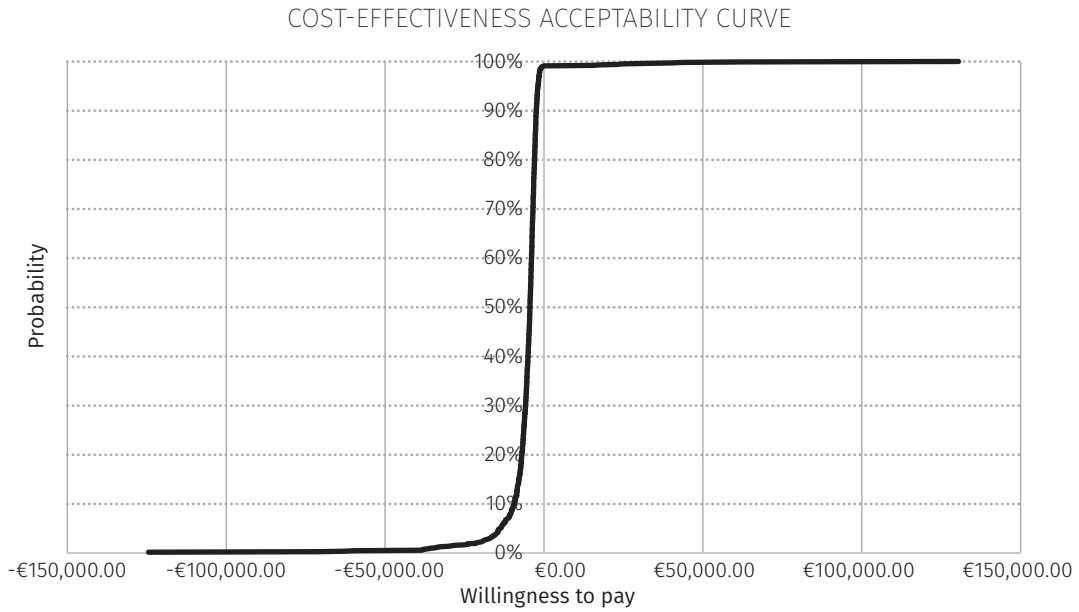
## FIGURE 3




The cost-effectiveness plane represents the differences in costs and QALYs between the treatment alternatives in the 1,000 simulations.

Reference: own elaboration.

## FIGURE 4




The acceptability curve represents the probability of acceptance of the 1,000 simulations with different thresholds.

Reference: own elaboration.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## DISCUSSION

According to this model, tapentadol PR generates more QALYs and less costs than oxycodone/naloxone PR. In addition to the drug costs savings associated with tapentadol PR, the improved tolerability profile of tapentadol PR allows savings by reducing the frequency of adverse events and treatment discontinuation. Indeed, combining two synergistic mechanisms of analgesic action, activation of μ-opioids receptors and inhibition of neuronal reuptake of noradrenaline, reduced typical opioid related gastrointestinal adverse events in clinal practice[9,10,13,40].

This study also shows that tapentadol PR could be a cost-effective strategy for treating musculoskeletal chronic pain in patients in need of a strong opioid in Spain as the ICER estimated by the model is included within the WTP threshold established for Spain (€25,000/QALY)[37,38]. Furthermore, the SNHS could be saving €179.54 per patient/year if treating with tapentadol PR rather than oxycodone/naloxone PR.

Sensitivity analyses were performed to assess the robustness of the results. Across all univariate DSA, tapentadol PR remained the dominant alternative. Our findings share similarities with other previously published studies. A study in the UK carried out in 2012 has shown that initiating 2nd line treatment with tapentadol PR instead of oxycodone controlled released in patients with severe non-malignant chronic pain was associated with less cost and improved quality of life[41]. Likewise, tapentadol PR was cost effective in Italy as a first line treatment for patients with musculoskeletal pain in need of a strong opioid[42]. These findings are consistent with our study and consolidate our conclusion. Our study is the first cost-effectiveness study to evaluate tapentadol PR for musculoskeletal pain in Spain. Another study carried out by Obradovic et al, evaluated tapentadol in severe chronic non-malignant pain compared to oxycodone, morphine and transdermal fentanyl. Although the type of pain is different, this study has shown similar results. Compared with morphine and transdermal fentanyl, tapentadol yielded incremental cost effectiveness ratios of €2,656 and €2,069 per QALY gained, respectively meanwhile compared to oxycodone, tapentadol was dominant[14].

This study has some limitations. Firstly, as our model does not include a death state, it omits all the patients who could have died during the time horizon which could create bias. Another potential limitation concerns the utilities used to populate the model. The same utility value was used for the on-treatment state for tapentadol PR and for oxycodone/naloxone PR. This might not reflect entirely the reality as tapentadol PR offers a better quality of life to patients than oxycodone/naloxone PR as reported by Baron et al[13]. This has also been confirmed in a recent real-world study analysing medical data from German patients with chronic LBP unsuccessfully treated with WHO-I/II analgesics. Patients treated with tapentadol PR improved to a greater extent their quality of life (both physically and mentally) compared to patients treated with WHO-III PR opioid analgesics including oxycodone ± naloxone[40]. Moreover, the clinical data used to populate the model come from the literature rather than from real world study. In this model, the time horizon at which tapentadol PR cost effectiveness is evaluated is quite short. This is a limitation as it does not establish whether tapentadol PR will be cost effective in the long term. Furthermore, the costs used in the model are the ones available from public databases and may not reflect the real clinical practice. Indeed, some costs might vary drastically from one hospital to another which could impact our estimations. Finally, this study does not consider indirect costs and therefore omit substantial savings that tapentadol PR could have generated in term of productivity loss. As reported per Baron et al, tapentadol PR significantly improved general health, physical functioning and vitality favouring the return to work[13]. Tapentadol PR value's might be underestimated as the model does not reflect the savings generated in term of sick leaves. To conclude, this model suggests that treating patients in need of a strong opioid with tapentadol PR for musculoskeletal chronic pain would be an effective and cost saving alternative for the SNHS.

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**Financiación**

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**Conflicto de intereses**

YIM, AGD, MD and AD are employees of Vivactis Weber, a company that received fees from Grünenthal Pharma for the development of this study. SAC is an independent consultant, who received a fee from Grünenthal Pharma. SRB is an employee of Grünenthal Pharma.


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