Clinical Drug Investigation (2021) 41:875–883
https://doi.org/10.1007/s40261-021-01074-x

ORIGINAL RESEARCH ARTICLE

Cost-Effectiveness Analysis of Tapentadol Versus Oxycodone/Naloxone in both Branded and Generic Formulations in Patients with Musculoskeletal Pain

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Accepted: 8 August 2021 / Published online: 15 September 2021

Abstract

Background and Objectives Current evidence shows that tapentadol hydrochloride prolonged-release is more cost effective than other opioids. However, the introduction into the market of generic formulations of traditional comparators, leading to potential savings due to their lower price, creates space for further research. The objective of this study is to evaluate and compare the efficacy of tapentadol versus oxycodone/naloxone and the economic impact of the two alternatives in both branded and generic formulations.

Methods A cost-effectiveness analysis was performed using the third-payer perspective (TPP), with specific reference to the Italian National Health Service. A Markov model was implemented to simulate transitions between states, comparing two arms: The first arm simulated the administration of tapentadol, while the second simulated the administration of oxycodone/naloxone, both branded and generic. The results were reported in terms of net monetary benefit (NMB). The willingness to pay (WPT) was estimated at €35,000/quality-adjusted life year.

Results Tapentadol was dominant in all scenarios, assuming a population of 1000 individuals over a 1-year time horizon. In all cases, although the prices of oxycodone/naloxone generic formulations were lower, the costs associated with treatment discontinuation were always higher than those associated with tapentadol. The comparison with the branded formulation of oxycodone/naloxone was associated with the highest savings of €431.77 per patient, and with the highest NMB of €1943.77 per patient.

Conclusion The results of this pharmacoeconomic evaluation promote the use of tapentadol in comparison with oxycodone/naloxone, confirming the results obtained in previous studies with reference to the generic formulations.

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Key Points

Tapentadol is an atypical opioid acting both as a μ-opioid receptor (MOR) agonist and as a noradrenaline reuptake inhibitor (NRI).

Tapentadol's efficacy has been proved in both the nociceptive and neuropathic components of chronic maladaptive pain.

The administration of tapentadol was associated with the highest savings and net monetary benefit.

1 Introduction

Pain is the most common symptom of musculoskeletal disorders. Low back pain (LBP) is one of the most frequent chronic pain conditions worldwide, with a lifetime prevalence > 70 % in western countries and a heavy burden for the healthcare system. Indeed, LBP is now considered the leading cause of disability worldwide. Remarkably, more than two out of three patients who experience acute LBP ultimately develop chronic LBP [1, 30–33].

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" [2]. Musculoskeletal pain can be caused by bones, joints, muscles, tendons, ligaments, and bursa disorders, or by a combination of these. Injuries are the most common cause of pain [25].

Musculoskeletal conditions affect one in four adults across Europe [4]. The prevalence of musculoskeletal pain increases up to 65 years of age [13–15]. LBP is the most common type of musculoskeletal pain. The 'Global Burden of Disease' report of 2019 states that LBP ranks 9th among disability causes, resulting from a complex interaction among psychological and social factors as well as patient comorbidities, in the comprehensive evaluation of all age ranges in terms of disability-adjusted life years (DALYs) [14, 15]. DALYs are used as a measure, periodically calculated and revised, of population health, representing the sum of years of life lost (YLLs) and years lived with disability (YLDs). Picavet and Shouten [3] observed in 2003 that in the Netherlands pain complaints were associated with limitations in daily living in three out of ten cases.

The duration of pain is one of the criteria for defining chronicity. In general, 3 months of persistent pain is considered as the threshold [28]. Furthermore, chronic pain should be regarded as a continuum with an inherently uncertain prognosis since it depends on many variables and has intrinsically multidimensional nature within the well-established interpretative bio-psycho-social model [5, 6]. The incidence of chronic musculoskeletal pain has been calculated to be 8.3% per year [7–9]. Notwithstanding such remarkably high incidence, the recovery rate is high, with an average incidence of 5.4%.

Musculoskeletal pain is common in all population subgroups and has extensive consequences on health, work, and the use of healthcare [7]. The Eurobarometer Report (2007), from a survey on health in the European Union, offered relevant information on the diffusion and magnitude of musculoskeletal pain in the European Union [10]. In general terms the prevalence of chronic pain in Italy is 28 % [12] and specifically that of musculoskeletal conditions is 26.7% [4].

The highest prevalence of disability associated with musculoskeletal pain emerged in Austria (35%) and Finland (33%), while the lowest prevalence values have been reported in Greece (13%), Ireland, and Luxemburg (16%).

Further evidence shows that in adults, LBP is the main reason for premature exit from the workforce [11].

Musculoskeletal conditions are the leading cause of disability worldwide and have a large impact on many other aspects of older people's health. Disabilities such as low physical activity level, poor mobility, frailty, depression, cognitive impairment, falls and poor sleep quality [8].

Opioid analgesics have demonstrated efficacy for the management of chronic osteoarthritis pain, as well as LBP, and are recommended for the management of chronic pain in patients who have failed to respond to other analgesics [17].

The clinical use of opioids can introduce different problems related to their proper prescription and to the adequate management of possible adverse reactions. However, the introduction of fixed-dose combinations of oxycodone/naloxone improved the treatment options. Tapentadol is an atypical opioid acting both as a μ-opioid receptor (MOR) agonist and as a noradrenaline reuptake inhibitor (NRI), thereby generating synergistic analgesic action [18]. Its efficacy has been confirmed in both the nociceptive and neuropathic components of chronic maladaptive pain [29], defined as dysfunctional pain disproportionate to the actual tissue damage, which persists long after the tissues have healed; thus, becoming a disease itself [19]. The combination of oxycodone/naloxone extended release (ER) at a fixed dose combination, with a ratio of 2:1, was designed to reduce opioid-induced constipation (OIC) by associating oxycodone, which provides analgesia, with naloxone, which prevents its binding or displaces it from the opioid receptors located in the gut wall [20]. This drug combination was shown to improve bowel function, as measured by the bowel function index, compared with oxycodone controlled release (CR), and to generate a statistically significant analgesic effect [20].

Current evidence shows that tapentadol is more cost effective than other opioids [21, 24, 25]. However, the introduction into the market of generic formulations of traditional comparators (other strong opioids), leading to potential savings due to their lower price, creates space for further research. The aim of this study was to investigate the cost effectiveness of tapentadol ER in branded formulations compared with the oxycodone/naloxone combination, in both its branded and generic formulations, in the treatment of chronic musculoskeletal pain in the Italian context.

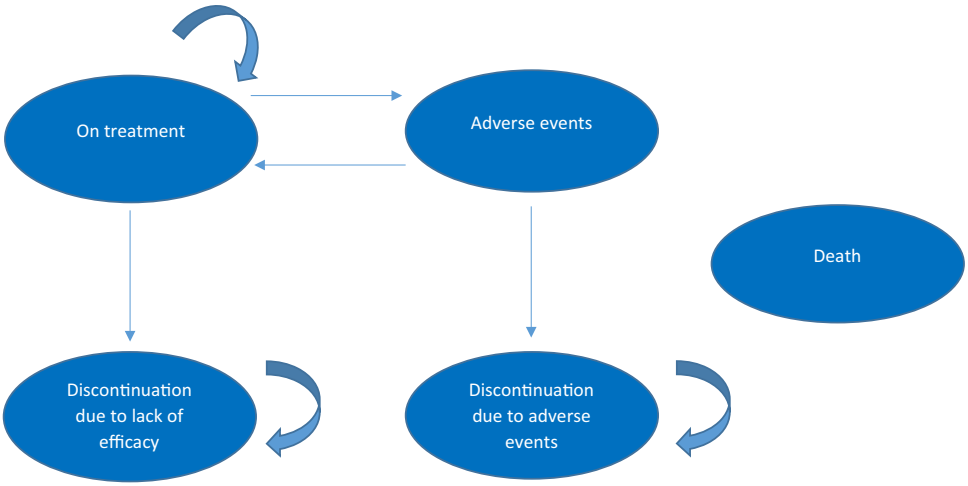

Fig. 1 Markov model

2 Methods

2.1 Model Structure and Hypothesis

The cost-effectiveness analysis was performed using the third-payer perspective (TPP), with specific reference to the Italian National Health Service. A Markov model was implemented to simulate transitions between states, comparing two arms: the first arm simulated the administration of tapentadol, while the second simulated the administration of oxycodone/naloxone, both branded and generic. This model is based on data from a comparative study [16] and is readapted from a previous economic evaluation [21]. Efficacy and safety data, which populated the model, were extrapolated from comparative clinical studies on both tapentadol and oxycodone/naloxone. The Markov model allows evaluating the changes in patient health conditions over time as a consequence of treatment. This model consisted of a hypothetical cohort of 1000 individuals. The model included four different health states: treatment, adverse events, discontinuation of treatment due to lack of efficacy or appearance of adverse events, and death (Fig. 1). Transition probabilities were adapted in order to be homogeneous with the 1-year time horizon and to make the model consistent with both the reference clinical trials and the previously published study [21], reporting treatment cycles in a 15-week period. Therefore, the duration of the model cycles was 90 days (12 weeks), when patients on treatment could: (1) still be on treatment; (2) manifest adverse reactions, such as nausea, vomiting, constipation, and headache; (3) discontinue the treatment due to inefficacy; or (4) discontinue the treatment due to the appearance of adverse reactions. The time horizon of the model was one year. Table 1 shows the detailed transition probabilities used to define the two arms of the model. The direct comparison used for the simulation of the two arms consisted into both looking for efficacy data in existing clinical trials that compared oxycodone/naloxone [16, 34] and a direct comparison using a Bayesian approach, this is, by using random distributions in order to fit the effectiveness of the different treatment under the assumption that generic and branded formulations of oxycodone/naloxone have the same effectiveness.

2.2 Utilities, Costs and Discount Rate

The utility coefficients were extrapolated from the literature [17]. The treatment costs and the costs associated with different health states were extrapolated from both the literature and the National Pharmaceutical Formulary, while visits and diagnostic examinations were extrapolated from the Italian tariff structure for outpatient services. The data used to populate the model, including the costs associated with each treatment for both generic and branded formulations of oxycodone/naloxone, are reported in Table 1.

Concerning the costs associated with treatment discontinuation as a consequence of adverse events or lack of efficacy (Table 2), the model considers as direct costs: medication, visits, access to ER, radiography, CT scan, MRI, surgery, nerve block injection, and epidural pain blockade. The costs of the treatments were extrapolated from the Italian National Pharmaceutical Reference Book in line with the guidelines of the Italian Health Authority (AIFA) [26, 27]. A 3% annual discount rate was applied to costs and QALYs in order to consider the different distribution of costs and benefits over time.

2.3 Cost-effectiveness

The results were reported in terms of net monetary benefit (NMB) to correctly interpret results that include savings, which are expressed as negative incremental costs. The willingness to pay (WPT) was estimated at €35,000/QALY.

Table 1 Data included in the model

Transition probabilities [16, 21]				
	Adverse reaction		Discontinuation (adverse reaction)	Discontinuation (non-effective)
Tapentadol	0.223		0.2	0.061
Oxycodone/naloxone	0.179		0.406	0.133
COSTS (€ every 90-days) [16, 22, 23, 26]				
	Treatment	Adverse reaction	Discontinuation (adverse reaction)	Discontinuation (non-effective)
Tapentadol	147.6	1.63	379.33	379.33
Oxycodone/naloxone	99	3.38	379.33	379.33
QALYs [17]				
	In treatment	Adverse reaction	Discontinuation (adverse reaction)	Discontinuation (non-effective)
Tapentadol	0.67	0.61	0.4	0.51
Oxycodone/naloxone	0.67	0.61	0.4	0.51

Price of oxycodone/naloxone branded and generic forumlations [25]

	Targin	Dolstip	Elatrex	Elipsodox	Algalt
€/day	1.89	1.07	1.08	1.08	1.17
Treatment duration	90	90	90	90	90
€/cycle	170.1	96.3	97.2	97.2	105.3

QALYs quality-adjusted life years

Table 2 Data on unit and total costs for discontinuation

Tapentadol vs oxycodone/naloxone formulations					
Treatment	Total costs	Total QALYs	Incremental costs of tapentadol	Incremental QALYs of tapentadol	Net monetary benefit
Tapentadol	615,179.45 €	899			
Targin	1,046,950.05 €	856	−431,770.60 €	43	1,943,770 €
Dolstip	817,590.33 €	856	−202,410.89 €	43	1,714,410 €
Elatrex/elipsodox	820,387.40 €	856	−205,207.96 €	43	1,717,207 €
Algalt	845,561.03 €	856	−230,381.58 €	43	1,742,381 €

QALYs quality-adjusted life years

The formula to calculate the NMB was:

NMB = (INCREMENTAL QALYs tapentadol/oxycodone-naloxone) × €35,000 − (INCREMENTAL COSTS tapentadol/oxycodone-naloxone).

Furthermore, the results were combined with details on the price of each oxycodone/naloxone formulation, both branded and generic.

2.4 Sensitivity Analysis

Probabilistic sensitivity analysis was performed to assess the impact of the individual and simultaneous variation of the parameters on the model results. A beta distribution was implemented for the following parameters: effectiveness, epidemiology, utilities, and transition rates. Conversely, a

gamma distribution was employed for the cost parameters. A total of 1000 Monte Carlo simulations were processed and reported on a cost-effectiveness acceptability curve (CEAC).

2.5 Budget Impact Analysis

Budget impact analysis was performed to assess the financial impact of the introduction of tapentadol compared with oxycodone/naloxone, considering treatment, adverse events, and discontinuation costs. These costs are consistent with the Markov model results used in the cost-effectiveness analysis, and they were applied to a population of 1.2 million patients, following the actual epidemiologic estimates. In addition, the budget impact analysis evaluated hypotheses on market shares in relation to tapentadol and different formulations of oxycodone/naloxone, both branded and generic. Treatment prices and pharmaceutical costs of adverse events were considered over a 3-year time horizon. In this analysis, a 3% discount rate was applied.

3 Results

3.1 Case Study and Scenario Analysis

Table 3 shows the results obtained from the comparison between tapentadol and oxycodone/naloxone, considering the average price and including both branded and generic formulations. Tapentadol was dominant in all scenarios, assuming a population of 1000 individuals over a 1-year time horizon. In all cases, although the prices of oxycodone/naloxone generic formulations were lower, the costs associated with treatment discontinuation were always higher than those associated with tapentadol. Furthermore, the savings associated with tapentadol in comparison with the oxycodone/naloxone branded formulations were also due to the higher costs of the branded formulation. Therefore, the comparison with the branded formulation of oxycodone/naloxone was associated with the highest savings, €431.77 per patient, and with the highest NMB—€1943.77 per patient.

On the other hand, the comparison with the Dolstip generic formulation entails the lowest savings (€202.41 per patient) and the lowest NMB (€1498 per patient). On average, the use of tapentadol instead of oxycodone/naloxone allows saving €254.99 per patient and an NMB of €1714.4 per patient.

3.2 Sensitivity Analysis

The tornado diagram in Fig. 2 summarizes the results of the univariate sensitivity analysis. The graph is centered on the NMB related to the case study in order to clearly express its variations due to the variability of the single parameters. The gray bars show the variation in the NMB with respect to the minimum input value. The black bars represent the variation

Table 3 Comparison of tapentadol with oxycodone/naloxone in generic and branded formulations (hypothetical cohort of 1000 individuals)

Treatment	On treatment population	Year 1		Year 2		Year 3	
		Treatment cost	AE and discontinuation cost	Treatment cost	AE and discontinuation cost	Treatment cost	AE and discontinuation cost
WithTapentadol							
Tapentadol	600,000.00	379,485,231,084.41 €	163,380,015,628.90 €	242,727,520,039.37 €	514,709,485,468.49 €	154,567,462,763.90 €	741,088,588,951.04 €
Targin	120,000.00	70,352,104,506.37 €	70,901,118,554.22 €	22,588,766,086.40 €	177,306,633,029.12 €	7,163,535,392.92 €	211,649,186,945.51 €
Dolstip	120,000.00	39,828,969,217.89 €	70,901,118,554.22 €	12,788,349,054.21 €	177,306,633,029.12 €	4,055,546,492.29 €	211,649,186,945.51 €
Elattrex	120,000.00	40,201,202,575.07 €	79,494,498,814.39 €	12,907,866,335.09 €	198,844,692,308.46 €	4,093,448,795.95 €	237,367,746,724.38 €
Elispdodox	120,000.00	40,201,202,575.07 €	70,901,118,554.22 €	12,907,866,335.09 €	177,306,633,029.12 €	4,093,448,795.95 €	211,649,186,945.51 €
Agalt	120,000.00	43,551,302,789.65 €	70,901,118,554.22 €	13,983,521,863.01 €	177,306,633,029.12 €	4,434,569,528.95 €	211,649,186,945.51 €
Total	1,200,000.00	613,620,012,748.45 €	526,478,988,660.15 €	317,903,889,713.17 €	1,422,780,709,893.42 €	178,408,011,769.96 €	1,825,053,083,457.45 €
Without Tapentadol							
Targin	240,000.00	140,704,209,012.73 €	141,802,237,108.43 €	45,177,532,172.81 €	354,613,266,058.23 €	14,327,070,785.83 €	423,298,373,891.02 €
Dolstip	240,000.00	79,657,938,435.78 €	141,802,237,108.43 €	25,576,698,108.42 €	354,613,266,058.23 €	8,111,092,984.57 €	423,298,373,891.02 €
Elattrex	240,000.00	80,402,405,150.13 €	158,988,997,628.79 €	25,815,732,670.18 €	397,689,384,616.93 €	8,186,897,591.91 €	474,735,493,448.77 €
Elispdodox	240,000.00	80,402,405,150.13 €	141,802,237,108.43 €	25,815,732,670.18 €	354,613,266,058.23 €	8,186,897,591.91 €	423,298,373,891.02 €
Agalt	240,000.00	87,102,605,579.31 €	141,802,237,108.43 €	27,967,043,726.02 €	354,613,266,058.23 €	8,869,139,057.90 €	423,298,373,891.02 €
Total	1,200,000.00	468,269,563,328.08 €	726,197,946,062.51 €	150,352,739,347.60 €	1,816,142,448,849.86 €	47,681,098,012.12 €	2,167,928,989,012.83 €

AE adverse event

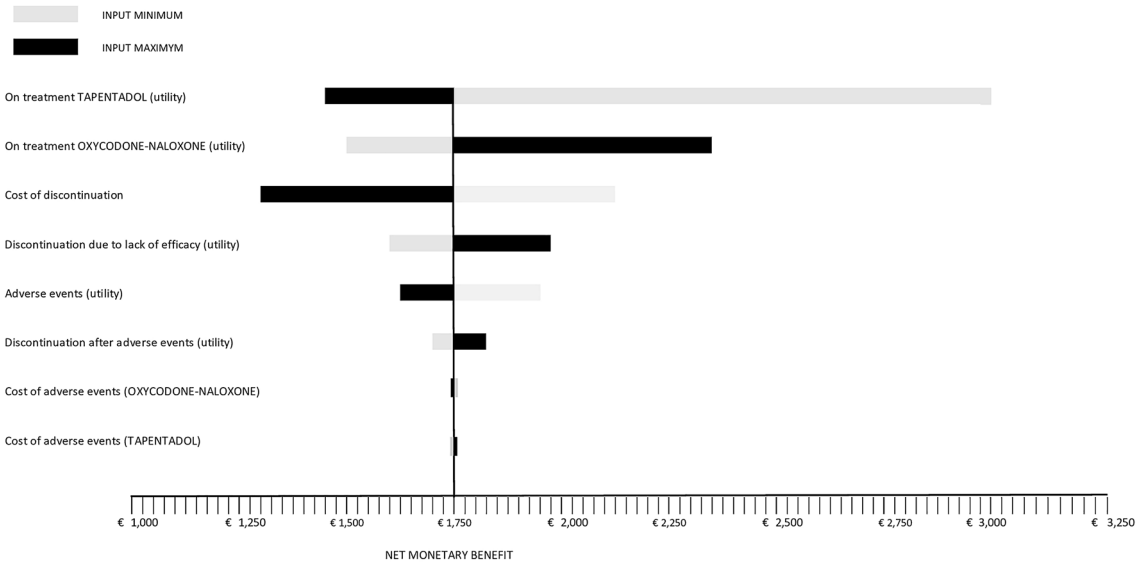

Fig. 2 Univariate sensitivity analysis

in the NMB when associated with the maximum input value. This analysis was performed on the basis of the AIFA perspective. In every scenario, variations that were dependent on the assessed parameters led to a positive NMB, implying that tapentadol remains dominant when compared with both branded and generic formulations of oxycodone/naloxone, regardless of the variations in the model parameters. The most sensitive parameters are utilities and discontinuation costs.

Figure 3 represents the cost-effectiveness plan resulting from the multivariate probabilistic sensitivity analysis of tapentadol versus oxycodone/naloxone. The simulation included all the formulations. This analysis shows that 53% of 1000 Monte Carlo simulations fall in the first quadrant of the cost-effectiveness plan, with tapentadol being dominant compared to oxycodone/naloxone. The same results are observed in Fig. 4, where the CEAC is represented, which shows that the use of tapentadol would lead to an NMB ranging from €1500 to €2400 per patient (25th–75th percentile). The 90th and 100th percentiles were associated with NMBs of €1000 and €2900 per patient, respectively.

3.3 Budget Impact Analysis

Table 4 shows the aggregated results of the budget impact analysis, which takes into consideration the pharmaceutical costs associated with tapentadol and with the different oxycodone/naloxone formulations available in the market. The results relate to the hypothesis that 25% of the market share is attributed to tapentadol. The remaining 75% of the market share was equally distributed among the other treatments.

Table 4 Development of the budget impact analysis

Cost items	Frequency	Unit costs	Total costs
GP visits	1.73	€ 20.66	€ 35.76
Specialist examination	0.29	€ 191.50	€ 55.24
NSAIDs (average price of 1 cycle)	1.00	€ 6.60	€ 6.60
Physiotherapy sessions	5.00	€ 50.00	€ 250.00
Emergency visits	0.14	€ 270.00	€ 38.94
Hospitalization	0.06	€ 674.00	€ 38.88
Total			€ 425.43

The introduction of tapentadol generates savings for slightly less than €23 million in the first year. This amount increases to more than €99 million in the second year and approximately €89 million in the third year.

If tapentadol owned 50% of the market share, saving would amount to approximately €46 million in Year 1, €198 million in Year 2, and €176 million in Year 3.

4 Discussion

The results of this pharmacoeconomic evaluation encourage the use of tapentadol in comparison with oxycodone/naloxone, confirming the results obtained in previous studies with reference to the generic formulations.

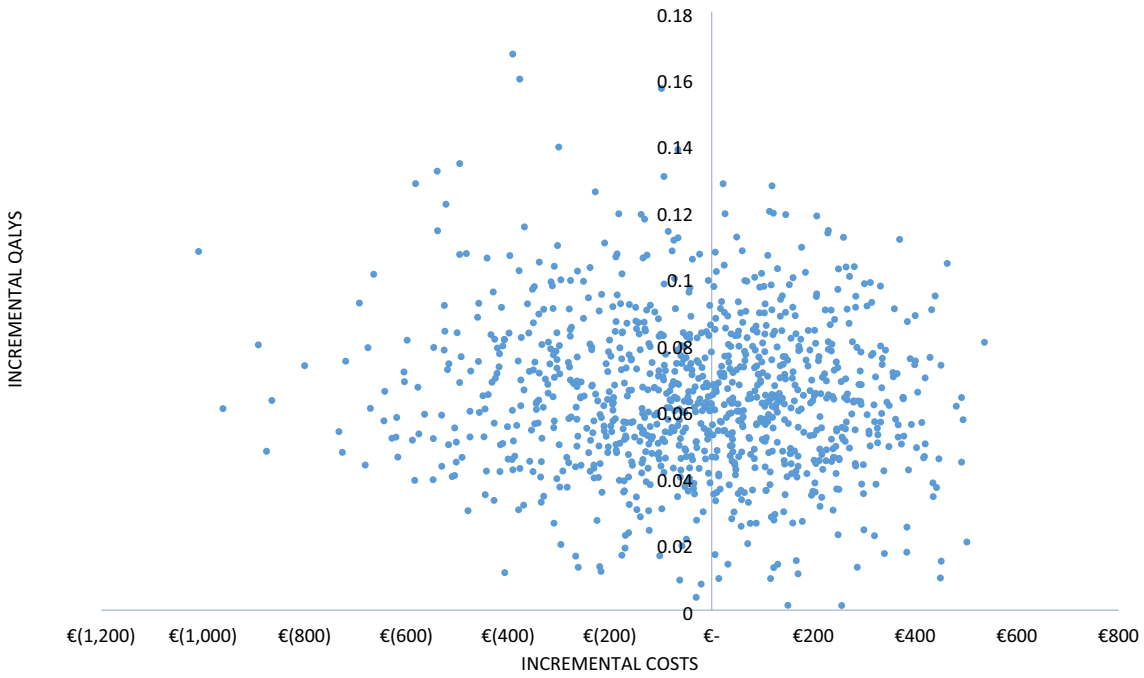

Fig. 3 Probabilistic sensitivity analysis: cost effectiveness plan according to NHS perspective. *QALYs* quality-adjusted life years, *CE* cost effectiveness

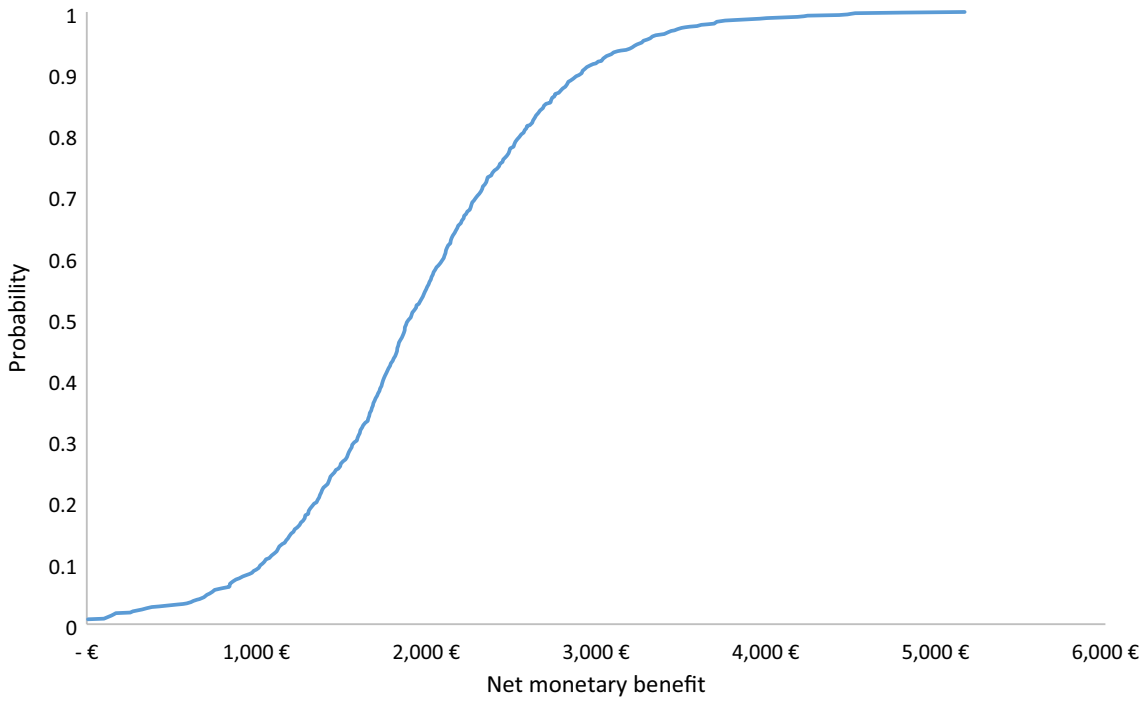

Fig. 4 Cost effectiveness acceptability curve (CEAC)

In 2014, Coluzzi and Ruggeri [21] performed a clinical and economic evaluation of tapentadol and oxycodone/naloxone association compared with oxycodone for musculoskeletal pain, demonstrating that tapentadol offers enhanced clinical outcomes at lower costs. Similar results were reported by Obradovic et al. [25] in 2012. The current study confirms such outcomes: Tapentadol was dominant in 100% of cases, according to the National Health System perspective.

Ikenberg et al. [24] compared the cost-effectiveness of tapentadol with oxycodone in patients with severe non-malignant chronic pain. The results that emerged from their Markov model showed that tapentadol improved patients' quality of life and was less costly compared to branded oxycodone, as confirmed by the incremental cost-effectiveness ratio (ICER).

Baron et al. [16], in 2016, compared the effectiveness of tapentadol versus oxycodone/naloxone PR in patients with severe chronic LBP. The study showed the superiority of tapentadol over oxycodone/naloxone in terms of analgesic efficacy in terms of both neuropathic pain-related symptoms and gastrointestinal tolerability. In 2010, Wild et al. [34], had already shown, in a long-term evaluation, a good tolerability profile of tapentadol, which, compared with oxycodone, was associated with a lower incidence of gastrointestinal adverse events, particularly nausea, constipation, and vomiting.

For what concerns available pharmacological alternatives, there are many studies reporting different levels of efficacy of other pharmacological solutions that may treat LBP, but none of those studies included a cost-effectiveness analysis.

This study has limitations. The data are based on experts' opinion while it would have been preferable to have data coming from administrative databases. In addition, clinical data comes from the literature rather than real world data. Further, heterogeneity is not considered, that is, the different base line characteristics of patients. Finally, compliance was not considered, for it primarily applies to oxycodone/naloxone formulations due to the higher discontinuation rate as a consequence of adverse reactions. Therefore, considering compliance would have only improved the dominance of tapentadol in comparison to other alternatives.

The strength of this study, in comparison to other similar studies, is that it includes the comparison of all types of formulations of tapentadol and oxycodone/naloxone (branded and generic).

5 Conclusion

Based on the economic evaluations of this study, tapentadol was shown to provide an enhanced effect in terms of quality of life at lower costs, compared with oxycodone/naloxone. Despite the results obtained from the budget impact analysis of pharmaceutical expenditures, tapentadol is costlier than the generic formulations of oxycodone/naloxone. However, tapentadol is dominant for Italian National Health Service compared with other drugs, in both branded and generic formulations, when discontinuation costs are also taken into consideration.

Declarations

Funding This research was entirely funded by Grünenthal GmbH. The views expressed in this document are those of the authors and do not necessarily correspond to the views of the funders. The study was realized with an unconditional grant by Grunenthal Italia.

Disclosure All authors declare that they have no competing interests.

Conflict of interest All the authors and contributors to this study—M Ruggeri, A Signorini, S Caravaggio, C Santori, F Rosiello, F Coluzzi,—declare to have no competing interests.

Ethics approval No ethics approval was needed for this study as no clinical patients were involved.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material The data produced and analyzed in this study are available from the corresponding author upon reasonable request.

Code availability Not applicable.

Author contributions MR, study design and analysis; AS, analysis and writing of the paper; SC, analysis and writing of the paper; SC, part of the analysis; FR, discussion and interpretation of results; FC, discussion and interpretation of results.

Disclaimer Matteo Ruggeri did not receive any funding for the involvement in this study. The views expressed in this paper do not necessarily represent the one of the Istituto Superiore di Sanità.

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